



No. 08-133462- -00002-0000

Fecha: 2009-07-31 15:03:51 Dep. 2020 NUECREACION
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 400 OPOSIOBSERVTER Folios: 49

FORMULARIO ÚNICO DE OPOSICIÓN

①

OPOSICIÓN A:

- | | |
|--|--|
| ☒ Patente de Invención. | ☐ Marca Colectiva. |
| ☐ Patente de Modelo de Utilidad. | ☐ Marca de Certificación. |
| ☐ Diseño Industrial. | ☐ Lema Comercial. |
| ☐ Esquema de Trazado para Circuitos Integrados. | |
| ☐ Marcas de Productos o Servicios. | |

②

Número del expediente: 08-133462

Solicitante: NOVARTIS AG.

SOLICITUD
PUBLICADA

Apoderado: CARLOS REYNALDO OLARTE GARCIA

Título de la nueva creación o denominación del signo: FORMULACIONES

GALENICAS DE ALISQUIRENO E HIDROCLOROTIAZINA

Gaceta: 603

③ OPOSICIÓN PRESENTADA POR:

SOLICITANTE	Nombre: <u>GYNOPHARM S.A.</u>	IDENTIFICACIÓN	
	Dirección: <u>Carrera 14 N° 94-44 Piso 7 Torre b</u>	C.C. ☐	NIT ☒
	Nacionalidad o Domicilio: <u>COLOMBIA</u>	C.E. ☐	Otro ☐
	Lugar de Constitución: <u>BARRANQUILLA</u>	Cual <u> </u>	
	Teléfono: <u>2 36 84 95</u> Fax: <u> </u>	Número <u>802,006,279-4</u>	
	E-mail: <u> </u>		
REPRESENTANTE O APODERADO	Nombre: <u>ELIANA ISAURA MORENO BOHORQUEZ</u>	IDENTIFICACIÓN	
	Dirección: <u>CARRERA 13 No. 119-95</u>	C.C. ☒	NIT ☐
	Teléfono: <u>(571)213 12 13</u> Fax: <u>(571)612 19 79</u>	C.E. ☐	Otro ☐
	E-mail: <u>negocios@optimum-co.com</u>	Cual <u> </u>	
		Número <u>51.975.664</u> TP <u>83823</u>	

④ FUNDAMENTOS DE LA OPOSICIÓN:

Art.14, 16, 18, 20 y 30 de la Decisión 486 de la CAN

Causal: No cumple con los requisitos de patentabilidad.

Signo opositor:

Justificación:

La presente solicitud no cumple con los requisitos de patentabilidad dado que lo
revelado, ya se encontraba en el estado de la técnica o es posible derivarlo de la
misma tal y como se demostrará en el capítulo "Fundamento de Hechos".

⑤ Comprobante de pago No. _____

Fecha _____

⑥ ANEXOS

- ☐ Comprobante de pago de la tasa.
- ☐ Poderes, si fuere el caso.
- ☐ Pruebas de los fundamentos de la oposición.
- ☐ Documentos que acrediten el legítimo interés, si fuere el caso.
- ☐ Documento que acredita la existencia y representación legal de las partes, cuando sean personas jurídicas.

⑦

NOMBRE: ELIANA ISAURA MORENO BOHORQUEZ

FIRMA: _____

C.C. 51'975.664

TP. 83823



Derecho de la Competencia, Propiedad
Industrial y Comercio Exterior

Señora Jefe,

DIVISIÓN DE NUEVAS CREACIONES

Superintendencia de Industria y Comercio

E. S. D.

Referencia : Expediente N° 08 133462 ✓
Asunto : Oposición a la solicitud de patente de Invención titulada
"FORMULACIONES GALENICAS DE ALISQUIRENO E
HIDROCLOROTIAZIDA"
Solicitante : NOVARTIS AG
Opositora : GYNOPHARM S.A.

Publicada en la Gaceta de la Propiedad Industrial
N° 603 del 30 de Abril de 2009

Yo, *ELIANA ISaura MORENO BOHORQUEZ*, abogada en ejercicio, identificada como aparece al pie de su firma, con tarjeta profesional No. 83823 del Consejo Superior de la Judicatura, en mi condición de apoderada de la sociedad *GYNOPHARM S.A.* conformada bajo las leyes de la República de Colombia y domiciliada en la ciudad de Barranquilla, Colombia, atentamente manifiesto que estando dentro del término de ley y por orden expresa de mi representada, presento oposición a la concesión del registro de la Patente de Invención titulada "FORMULACIONES GALENICAS DE ALISQUIRENO E HIDROCLOROTIAZIDA", cuyo titular es NOVARTIS AG, y pido a Usted declarar fundada esta oposición y en consecuencia negar el registro de la patente solicitada.

1. INTERÉS PARA ACTUAR ✓

Conforme a lo dispuesto en el artículo 42 de la Decisión 486 de 2000 de la CAN, estando dentro del término estipulado por la ley, manifiesto el legítimo interés de nuestra representada para oponerse al registro de la patente de la referencia, atendiendo a que la solicitud pretendida no cumple con los requisitos dispuestos en la ley como se analizará más adelante y de ser concedida afectaría directamente la comercialización de algunos productos de mi representada, que contienen, en particular HIDROCLOROTIAZINA. Por lo tanto, solicito respetuosamente a ese Despacho se sirva tener en cuenta la presente oposición dentro del trámite administrativo que se surte en esta Superintendencia.

2. FUNDAMENTOS DE HECHOS

2.1. La solicitud objeto de la presente fue presentada el 23 de enero de 2009 reivindicando prioridad bajo la solicitud GB20060012540 del 2006-06-23; y fue publicada en Colombia, en la Gaceta de la Propiedad Industrial N° 603 del 30 de Abril de 2009, cuya publicación internacional corresponde a la WO2007147596 del 2007-12-27.

2.2. La solicitud colombiana 08 133462 objeto de la presente oposición, se refiere a una forma de dosificación oral sólida, la cual comprende una cantidad terapéuticamente efectiva de alisquireno, o una sal farmacéuticamente aceptable del mismo, una cantidad terapéuticamente efectiva de hidroclorotiazida, y un relleno hidrofílico seleccionado a partir del grupo de un carbohidrato o combinaciones del

mismo, por ejemplo azúcares, alcoholes de azúcar, y almidones, o combinaciones de los mismos.

2.3. En primera instancia, se debe advertir que las reivindicaciones también se refieren al uso y a un método de tratamiento y no sólo a la composición farmacológica o a un método de fabricación mediante la cual se obtenga un producto tangible y según la legislación, decisión 486 de la Comunidad Andina de Naciones, Artículo 14.- *“Los Países Miembros otorgarán patentes para las invenciones, sean de producto o de procedimiento (...)”*, los usos no están contemplados como patentables; y, Artículo 20.- *“No serán patentables (...) d) los métodos terapéuticos o quirúrgicos para el tratamiento humano o animal, así como los métodos de diagnóstico aplicados a los seres humanos o a animales”*. Solo serán patentables los productos o procedimientos. Por lo tanto a luz de la norma, dicha materia referente al uso y a un método de tratamiento no sería patentable.

2.4. Ahora bien, con base en el artículo 14 de la Decisión 486 de la CAN consagra lo siguiente: *“Los países miembros otorgarán patentes para las invenciones, sean de producto o procedimiento, en todos los campos de la tecnología, siempre que sean nuevas, tengan nivel inventivo y sean susceptibles de aplicación industrial”*. Así las cosas, las invenciones objeto de patente deben ser nuevas y tener nivel inventivo. Bien, pues antes de la fecha de prioridad de esta solicitud se encuentran los siguientes documentos que afecta la patentabilidad de la presente solicitud:

- D1: WO03097098 publicada el 27 de noviembre de 2003.
- D1: US2005271720 publicada el 12 de diciembre de 2005.

2.5. Ahora bien, el documento D1, particularmente en la descripción revela una composición que incluye un inhibidor de renina y un bloqueador de canales de calcio (CCB) además de un diurético. Particularmente en la página 15, párrafo 3,

reivindicación 2 y 5 revela que la combinación puede comprender alisquireno e hidroclorotiazida (HCT). Como tal, el documento D2 se relaciona con composiciones farmacéuticas que contienen irbesartan, proveyendo formulaciones orales con una alta cantidad relativa o concentración de irbesartan. Particularmente en las páginas 5 tabla 6 y página 6, tablas 7 a 9, este documento D2, revela composiciones que comprenden hidroclorotiazida HCT y un almidón como relleno hidrófilico. Por lo tanto, para cualquier persona versada en la materia a partir de la materia definida en los documentos D1 de una composición que incluye alisquireno e hidroclorotiazida (HCT) en combinación con la materia referida en el documento D2 de una composición que incluye hidroclorotiazida HCT y un almidón como relleno hidrófilico puede llegar obviamente a una forma de dosificación oral sólida, la cual comprende una cantidad terapéuticamente efectiva de alisquireno, o una sal farmacéuticamente aceptable del mismo, una cantidad terapéuticamente efectiva de hidroclorotiazida, y un relleno hidrofílico. Así las cosas, como lo evidencia dicho documento D1 en combinación con el documento D2, la presente solicitud no comprende altura o nivel inventivo.

2.6. Por lo tanto, este documento objeto de oposición a la luz de los documentos D1 y D2 carece evidentemente de ALTURA O NIVEL INVENTIVO.

2.7. En consecuencia y de acuerdo a lo descrito anteriormente, se deriva que la solicitud colombiana 08 133462 no puede pretender un monopolio por patente toda vez que lo que pretende no cumple con dos de los tres requisitos necesarios para su protección.

2.8. Que por consiguiente, respecto a la solicitud pretendida se tiene que:

2.8.1. CARENCIA DE ALTURA INVENTIVA. Según la Decisión 486 de la Comunidad Andina de Naciones, Artículo 18.- "Se considerará que una invención

tiene nivel inventivo, si para una persona del oficio normalmente versada en la materia técnica correspondiente, esa invención no hubiese resultado obvia ni se hubiese derivado de manera evidente del estado de la técnica.”. A la fecha de prioridad, 23 de junio de 2006, a partir del documento D2 en combinación con D1, puede llegar de manera evidente a una forma de dosificación oral sólida, la cual comprende una cantidad terapéuticamente efectiva de alisquireno, o una sal farmacéuticamente aceptable del mismo, una cantidad terapéuticamente efectiva de hidroclorotiazida, y un relleno hidrofílico. Así las cosas, como lo evidencia dicho documento D1 en combinación con el documento D2, la presente solicitud no comprende altura o nivel inventivo, sobre el cual busca protección en el capítulo reivindicatorio.

2.8.2. CARENCIA DE APLICACIÓN INDUSTRIAL La Decisión 486 de la CAN consagra en su artículo 14 lo siguiente: “Los países miembros otorgarán patentes para las invenciones, sean de producto o procedimiento, en todos los campos de la tecnología, siempre que sean nuevas, tengan nivel inventivo y sean susceptibles de aplicación industrial”. La presente solicitud carece de aplicación Industrial ya que como se demostró anteriormente, algunas cláusulas reclaman el método terapéutico y estos no son aplicables industrialmente porque primero no se obtiene un producto o proceso; y segundo no es reproducible o repetible a escala industrial. Por lo tanto, el objeto de la presente invención referido a los usos y métodos terapéuticos, no cumplen con el requisito de la aplicación industrial.

2.9. Dado lo anterior, es posible deducir que la solicitud y lo reivindicado no es objeto de patentabilidad pues es contrario a lo que dicta la Decisión 486 de la Comunidad Andina de Naciones, Artículo 14.- “Los Países Miembros otorgarán

patentes para las invenciones, sean de producto o de procedimiento, en todos los campos de la tecnología, siempre que sean nuevas, tengan nivel inventivo y sean susceptibles de aplicación industrial.”. La solicitud pretendida no cumple con dos de los tres requisitos de patentabilidad.

2.10. Por todo lo anterior, atentamente solicito a usted que se sirva declarar fundada la presente oposición y negar el registro Patente de invención denominada **“FORMULACIONES GALENICAS DE ALISQUIRENO E HIDROCLOROTIAZIDA”**, cuyo titular es **NOVARTIS AG**, solicitud Colombiana que apareció publicada en la Gaceta de la Propiedad Industrial N° 603 del 30 de Abril de 2009.

3. PRUEBAS

De conformidad con lo dispuesto por las normas vigentes, solicito a usted tener como prueba en este asunto los siguientes:

- D1: WO03097098 publicada el 27 de noviembre de 2003.
- D1: US2005271720 publicada el 12 de diciembre de 2005.

4. FUNDAMENTO DE DERECHO

Fundamento esta observación en las normas legales siguientes:

- 4.1. Numeral 1 del artículo 586 del Código de Comercio.
- 4.2. Artículo 42 de la Decisión 486 de la Comisión del Acuerdo de Cartagena.
- 4.3. En las demás normas concordantes.

5. ANEXOS

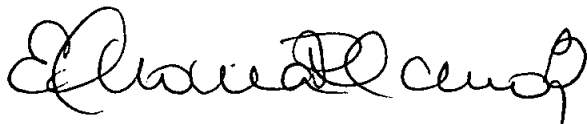
Para los efectos correspondientes anexo al presente escrito los siguientes documentos:

1. Poder para actuar en el presente.
2. Documento que acredita al representante legal de **GYNOPHARM S.A.**
3. Recibo de caja del respectivo pago de tasa.
4. Copias de los documentos:
 - DI: WO03097098 publicada el 27 de noviembre de 2003.
 - DI: US2005271720 publicada el 12 de diciembre de 2005.

6. NOTIFICACIONES

Para efectos de notificaciones que por disposición del artículo 50 del Decreto 01 de 1984 debe hacer su Despacho, informo que mi representada y la suscrita recibiremos notificaciones en la Secretaría de su Despacho o en mis oficinas situadas en la Carrera 13 N° 119-95, Of. 104 de esta ciudad de Bogotá.

Señor Superintendente,



ELIANA ISAURA MORENO BOHORQUEZ

C.C. 51'975.664 de Bogotá

T.P.A. 83823 del C.S. de la J.



Gynopharm

The primary support
for the woman's health specialist

PODER ESPECIAL

Yo, **LUIS PALACIOS ARAGÓN**, mayor de edad y vecino de la ciudad de Barranquilla (Colombia); identificado como aparece al pie de mi firma, quien en el presente documento actúa en calidad de Representante Legal de la sociedad **GYNOPHARM S.A.** sociedad legalmente constituida y domiciliada en la ciudad de Barranquilla (Colombia), por el presente documento otorgo a la doctora **ELIANA ISAURA MORENO BOHÓRQUEZ**, abogada en ejercicio, identificada como aparece al pie de su firma, con tarjeta profesional No. 83823 del C.S. de la J., poder especial, amplio y suficiente, para formular oposiciones u observaciones a la solicitud de patente No. 08 133462, titulada "**FORMULACIONES GALENICAS DE ALISQUIRENO E HIDROCLOROTIAZINA**", cuyo titular es **NOVARTIS AG**, publicada en la gaceta No. 603 del 30 de abril de 2009.

Nuestro apoderado queda facultado, de manera expresa, para realizar todo tipo de actos necesarios para llevar a cabo el trámite de la oposición, incluyendo, sin limitación, preparar y presentar solicitudes, hacer declaraciones, pagar tasas, contribuciones e impuestos, recabar los títulos o certificados. Asimismo quedan autorizados para impugnar administrativa y judicialmente todo lo que fuere resuelto en el expediente a que se hace expresa referencia en el presente poder, con todas las facultades generales y específicas que fuera requerido para ella.

De la misma manera, además de las facultades que le confiere la naturaleza del presente mandato, se encuentran facultados para recibir, desistir, transigir, sustituir, y reasumir el presente poder, incoar acciones, interponer recursos y demás facultades conferidas por la ley.

Dado y Firmado en Barranquilla (Colombia) a los ____ días del mes de ____ de 2009.

GYNOPHARM S.A.

Cédula de Extranjería: No. 319788.

NIT: 802.006.279-4

Representante Legal

Acepto:

ELIANA ISAURA MORENO BOHÓRQUEZ

C.C. 51'975.664 de Bogotá

T.P.A. 83823 del C.S. de la J.

R. 8-133462

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 08-133462-00002-0000

Fecha: 2009-07-31 15:03:51 Dep. 2020 NUECREACIONE
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 400 OPOSIOBSERVTER Folios: 49

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 09 - 59,590
FECHA : AGOSTO 12 DE 2009

***** CONSIGNACION *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
GYNOPHARM S.A.	RECIBO DE CAJA			56599	31/07/2009	540,000.00
GYNOPHARM S.A.	RECIBO DE CAJA			56600	31/07/2009	540,000.00
GYNOPHARM S.A.	RECIBO DE CAJA			56601	31/07/2009	540,000.00
GYNOPHARM S.A.	RECIBO DE CAJA			56602	31/07/2009	540,000.00

***** CONCEPTO *****

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-04	PRESENTACION DE OBSERVACIONES	
		12 MARCAS Y LEMAS COMERCIALES	287,000.00
		TOTAL :	\$ 287,000.00

SON: DOSCIENTOS OCHENTA Y SIETE MIL PESOS

RESPONSABLE : _____

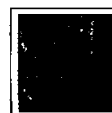
RECIBO DE CAJA APLICADO AL EXPEDIENTE No. _____



01



* 8 3 6 9 7 3 9 4 *



13

CERTIFICADO NACIONAL

CAMARA DE COMERCIO DE BARRANQUILLA

FECHA: 2009/07/30

HORA: 12:34:26

OPERACION: 10ERP0730125

PAGINA: 1

CERTIFICADO DE EXISTENCIA Y REPRESENTACION LEGAL O DE INSCRIPCION DE DOCUMENTOS.

EL SUSCRITO SECRETARIO DE LA CAMARA DE COMERCIO DE BARRANQUILLA, CON FUNDAMENTO EN LAS INSCRIPCIONES DEL REGISTRO MERCANTIL:

C E R T I F I C A

Que por Escritura Pública No. 3,551 del 17 de Dic/bre de 1997, otorgada en la Notaria 3a. de Barranquilla, inscrito(as) en esta Cámara de Comercio, el 18 de Dic/bre de 1997 bajo el No. 72,965 del libro respectivo, fue constituida la sociedad-----
anonima denominada GYNOPHARM S.A.-----

C E R T I F I C A

Que dicha sociedad ha sido reformada por las siguientes escrituras y/o documentos privados:

Numero	aaaa/mm/dd	Notaria	No. Insc o Reg	aaaa/mm/dd
532	1999/03/25	Notaria 3a. de Barranquilla	80,373	1999/04/13

C E R T I F I C A

Que de acuerdo con la(s) escritura(s) arriba citada(s), la sociedad se rige por las siguientes disposiciones:

DENOMINACION O RAZON SOCIAL:

GYNOPHARM S.A.-----

DOMICILIO PRINCIPAL: Barranquilla.

NIT No: 802.006.279-4.

MATRICULA MERCANTIL: 245,470.

C E R T I F I C A

Direccion para notificaciones judiciales:

CR 49.C No 80 - 125 OF 512.

De la ciudad de Barranquilla.

C E R T I F I C A

DURACION: El término de duración de la sociedad se fijó hasta el 16 de Dic/bre de 2047.

C E R T I F I C A

OBJETO SOCIAL: a) La fabricacion de capsulas y otro productos similares a partir de materiales tales como gelatinas u otros de distinta naturaleza, que puedan ser utilizados como envases o recipientes de productos y sustancias quimicas, farmaceuticas y cosmeticas, para

*** CONTINUA ***



01



* 8 3 6 9 7 3 9 5 *



13

CERTIFICADO NACIONAL

CAMARA DE COMERCIO DE BARRANQUILLA

FECHA: 2009/07/30

HORA: 12:34:26

OPERACION: 10ERP0730125

PAGINA: 3

general, realizar cualquier acto o negocio que sea necesario o conveniente para el desarrollo de su objeto social y para la mejor proteccion de sus intereses corporativos o lo de sus socios.-----

C E R T I F I C A

CAPITAL

Nro Acciones

Valor Acción

Autorizado

\$*****4,000,000,000 *****4,000,000 *****1,000

Suscrito

\$*****2,672,646,000 *****2,672,646 *****1,000

Pagado

\$*****2,672,646,000 *****2,672,646 *****1,000

C E R T I F I C A

ADMINISTRACION: Seran funciones de la junta directiva, entre otras: Autorizar cualquier acto o contrato cuya cuantia sea superior al equivalente en pesos Colombianos a cincuenta mil dolares de los Estados Unidos de America (US\$50.000.00), liquidados a la tasa de cambio representativa del mercado vigente el dia en que se surta la aprobacion y para enajenar o gravar bienes inmuebles y demas activos fijos de la sociedad, cualquiera que sea la cuantia de la transaccion. Las demas que le sean propias y no esten atribuidas a otro organo social y las que le correspondan en virtud de la ley. la sociedad tendra un Gerente General, quien ejercera la administracion y representacion legal de la sociedad y tendra las siguientes atribuciones, entre otras: Ejercer la representacion legal de la sociedad en todos los actos y contratos que se requieran para el desarrollo del objeto social, de conformidad con lo previsto en las leyes y en los presentes estatutos. Aprobar y celebrar en nombre de la sociedad todo acto o contrato cuya cuantia sea igual o inferior al equivalente en pesos Colombianos a cincuenta mil dolares de los Estados Unidos de America (US\$50.000.00), liquidados a la tasa de cambio representativa del mercado vigente el dia en que se surta la aprobacion o celebracion del acto. Para enajenar, a cualquier titulo, bienes inmuebles de la sociedad o constituir gravámenes sobre los mismos, debera obtener la aprobacion de la junta directiva, cualquiera que sea la cuantia de la transaccion; o las demas funciones que le corres-

*** CONTINUA ***



01



* 8 3 5 9 7 3 9 5 *



14

CERTIFICADO NACIONAL

CAMARA DE COMERCIO DE BARRANQUILLA

FECHA: 2009/07/30

HORA: 12:34:26

OPERACION: 10ERP0730125

PAGINA: 5

Junta Directiva en Barranquilla, de la sociedad: GYNOPHARM S.A. cuya parte pertinente se inscribió en esta Cámara de Comercio, el 11 de Marzo de 2008 bajo el No. 138,342 del libro respectivo, fueron hechos los siguientes nombramientos:

Cargo/Nombre	Identificación
Suplente del Gerente.	
Mollajoli Centurion Andres Fernando	CE.*****351,283

C E R T I F I C A

Que según Acta No. 19 del 30 de Abril de 2009 correspondiente a la Asamblea de Accionistas en Barranquilla, de la sociedad: GYNOPHARM S.A. cuya parte pertinente se inscribió en esta Cámara de Comercio, el 27 de Mayo de 2009 bajo el No. 149,314 del libro respectivo, fueron hechos los siguientes nombramientos:

Cargo/Nombre	Identificación
Revisor Fiscal.	
PENALOSA AUDITORES & ASOCIADOS S.A.	Ni.*****830,095,635

C E R T I F I C A

Que por Documento Privado del 11 de Mayo de 2009, otorgado en Bogota por Peñalosa Auditores & Asociados S.A. inscrito en esta Cámara de Comercio, el 27 de Mayo de 2009 bajo el Nro 149,315 del libro respectivo, fueron hechos los siguientes nombramientos:

Cargo/Nombre	Identificación
Designado: Revisor Fiscal Ppal	
Padilla Romero Ivan Dario	CC.*****80,025,798
Designado: Revisor Fiscal Suplente	
Gomez Preciado Clara Judith	CC.*****52,544,226

C E R T I F I C A

Que según Documento Privado de fecha 10 de Octubre del 2.000, inscrito en esta Camara de Comercio el 23 de Noviembre del 2.000 bajo el No. 1.872 del libro repectivo, consta que el señor RUBEN MINSKI GONTOVNIK C.C. No. 7.463.982, actuando como Presidente y representante legal de la sociedad GYNOPHARM S.A., otorga Poder Especial, Amplio y Suficiente a KAREN JENNIFER FIGUEROA GARCIA C.C. No. 32.-732.070, para que en nombre y representacion de la sociedad suscriba todas las declaraciones cambiarias a que esta obligada GYNOPHARM

*** CONTINUA ***

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
27 November 2003 (27.11.2003)

PCT

(10) International Publication Number
WO 03/097098 A1

(51) International Patent Classification⁷: **A61K 45/06**
A61P 9/00

(US). **WEBB, Randy, Lee** [US/US]; 17 Honeyman Drive,
Flemington, NJ 08822 (US).

(21) International Application Number: PCT/EP03/05188

(74) Agent: **GRUBB, Philip**; Novartis AG, Corporate Intellectual Property, CH-4002 Basel (CH).

(22) International Filing Date: 16 May 2003 (16.05.2003)

(25) Filing Language: English

(26) Publication Language: English

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(54) Title: PHARMACEUTICAL COMPOSITION COMPRISING A RENIN INHIBITOR, A CALCIUM CHANNEL BLOCKER AND A DIURETIC

(57) Abstract: The invention relates to a pharmaceutical composition comprising (i) a renin inhibitor, (ii) a calcium channel blocker (CCB), and (iii) a diuretic and to a method of treatment of a condition or a disease selected from the group consisting of hypertension, heart failure such as (acute and chronic) congestive heart failure, left ventricular dysfunction and hypertrophic cardiomyopathy, diabetic cardiac myopathy, supraventricular and ventricular arrhythmias, atrial fibrillation, atrial flutter, detrimental vascular remodeling, myocardial infarction and its sequelae, atherosclerosis, angina (whether unstable or stable), renal insufficiency (diabetic and non-diabetic), heart failure, angina pectoris, diabetes, secondary aldosteronism, primary and secondary pulmonary hypertension, renal failure conditions, such as diabetic nephropathy, glomerulonephritis (including IgA nephropathy), renal fibrosis, scleroderma, glomerular sclerosis, proteinuria of renal disease, and also renal vascular hypertension, diabetic retinopathy, the management of other vascular disorders, such as migraine, peripheral vascular disease, Raynaud's disease, luminal hyperplasia, cognitive dysfunction (such as Alzheimer's), glaucoma and stroke, pulmonary and hepatic fibrosis, fibrotic diseases resulting from accumulation of excess extracellular matrix induced by TGF β and proliferative diseases of smooth muscle cells, including uterine fibroids comprising administering a therapeutically effective amount of said pharmaceutical composition to a mammal in need of such treatment.



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PHARMACEUTICAL COMPOSITION COMPRISING A RENIN INHIBITOR, A CALCIUM CHANNEL
BLOCKER AND A DIURETIC

The renin angiotensin system (RAS) is a complex hormonal system comprised of a large molecular weight precursor, angiotensinogen, two processing enzymes, renin and angiotensin converting enzyme (ACE), and the vasoactive mediator angiotensin II (Ang II) (J. Cardiovasc. Pharmacol., 15(Supp B) (1990) p. S1-S5). The enzyme renin catalyzes the cleavage of angiotensinogen into the decapeptide angiotensin I, which has minimal biological activity on its own and is converted into the active octapeptide Ang II by ACE. Ang II has multiple biological actions on the cardiovascular system, including vasoconstriction, activation of the sympathetic nervous system, stimulation of aldosterone production, antinatriuresis, stimulation of vascular growth (i.e., stimulation of smooth muscle cell proliferation and the deposition of excess extracellular matrix material in the vascular wall), and stimulation of cardiac growth. Ang II functions as a pressor hormone and is involved in the pathophysiology of several forms of hypertension.

The vasoconstrictive effects of angiotensin II are produced by its action on the non-striated smooth muscle cells, the stimulation of the formation of the adrenergic hormones epinephrine and norepinephrine as well as the increase of the activity of the sympathetic nervous system as a result of the formation of norepinephrine. Angiotensin II also has an influence on electrolyte balance, produces e.g. antinatriuretic and antidiuretic effects in the kidney and thereby promotes the release of, on the one hand, the vasopressin peptide from the pituitary gland and, on the other hand, of aldosterone from the adrenal glomerulosa. All these influences play an important part in the regulation of blood pressure, in increasing both circulating volume and peripheral resistance. Angiotensin II is also involved in cell growth and migration and in extracellular matrix formation.

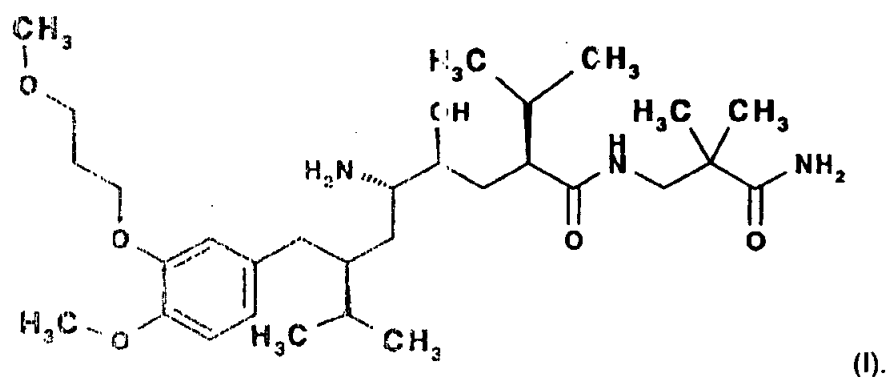
Angiotensin II interacts with specific receptors on the surface of the target cell. It has been possible to identify receptor subtypes that are termed e.g. AT1- and AT2-receptors. In recent times great efforts have been made to identify substances that bind to the AT1-receptor. Such active ingredients are often termed angiotensin II antagonists. Because of the inhibition of the AT1-receptor such antagonists can be used e.g. as antihypertensives or for the treatment of congestive heart failure, among other indications. Angiotensin II

antagonists are therefore understood to be those active ingredients that bind to the AT1-receptor subtype.

Inhibitors of the renin angiotensin system are well known drugs that lower blood pressure and exert beneficial actions in hypertension and in congestive heart failure as described, for example, in N. Eng. J. Med. 316, 23 (1987) p. 1429-1435. A large number of peptide and non-peptide inhibitors of the renin angiotensin system are known, the most widely studied being the ACE inhibitors, which include the drugs captopril, enalapril, lisinopril, benazepril and spirapril. Although a major mode of action of ACE inhibitors involves prevention of formation of the vasoconstrictor peptide Ang II, it has been reported in Hypertension, 16, 4 (1990) p. 363-370 that ACE cleaves a variety of peptide substrates, including the vasoactive peptides bradykinin and substance P. Prevention of the degradation of bradykinin by ACE inhibitors has been demonstrated, and the activity of the ACE inhibitors in some conditions has been reported in Circ. Res., 66, 1 (1990) p. 242-248 to be mediated by elevation of bradykinin levels rather than inhibition of Ang II formation. Consequently, it cannot be presumed that the effect of an ACE inhibitor is due solely to prevention of angiotensin formation and subsequent inhibition of the renin angiotensin system.

In addition to inhibiting the conversion of angiotensin I to angiotensin II, or blocking the AT1 receptor, the RAS can be stopped at the beginning of its pathway. This initial step (i.e., the conversion of angiotensinogen to angiotensin I) is mediated by renin and can be inhibited by renin inhibitors (RI). Renin inhibitors fully shut down the formation of angiotensin II because they act on the rate-limiting step in the cascade. Because of the virtually complete blockage of angiotensin II formation with RI, these agents can be demonstrated to have improved efficacy over ACE inhibitors or blockers of the AT1 receptor. Furthermore, because of their high degree of specificity, RI are associated with less side effects than ACE inhibitors. One such RI is aliskiren. Others are detikiren, terlakren, and zankiren.

Aliskiren has the following chemical formula (I)



The renin inhibitor of formula (I), chemically defined as 2(S),4(S),5(S),7(S)-N-(3-amino-2,2-dimethyl-3-oxopropyl)-2,7-di(1-methylethyl)-4-hydroxy-5-amino-8-[4-methoxy-3-(3-methoxypropoxy)phenyl]-octanamide, is specifically disclosed in EP 678503 A. Especially preferred is the hemi-fumarate salt thereof.

A drawback in the treatment of hypertension and diseases and conditions related thereto is that monotherapy frequently stimulates compensatory reflexes that counteract the pharmacologically-induced reduction in blood pressure. This compensation tends to hinder successful blood pressure lowering. It is therefore desirable to develop additional means of treatment for this application.

The present invention relates to a pharmaceutical composition comprising (i) a renin inhibitor, (ii) a calcium channel blocker (CCB), and (iii) a diuretic, or, where appropriate, in each case a pharmaceutically acceptable salt thereof, especially for the treatment of a disease or condition as set forth hereinbefore or hereinafter.

The invention likewise relates to the use of (i) a renin inhibitor, (ii) a calcium channel blocker (CCB), and (iii) a diuretic, or, where appropriate, in each case a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for the treatment of a disease or condition as set forth hereinbefore or hereinafter.

The invention likewise relates to a method for the treatment of a disease or conditions as set forth hereinbefore or hereinafter comprising administering to an animal, including man, a therapeutically effective amount of (i) a renin inhibitor, (ii) a calcium channel blocker (CCB),

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and (iii) a diuretic, or, where appropriate, in each case a pharmaceutically acceptable salt thereof.

The present invention furthermore relates to a kit of parts comprising
(i) a pharmaceutical composition of a renin inhibitor or a pharmaceutically acceptable salt thereof, (ii) a pharmaceutical composition of a calcium channel blocker (CCB) or a pharmaceutically acceptable salt thereof, and (iii) a pharmaceutical composition of a diuretic, or a pharmaceutically acceptable salt thereof,
in the form of two or three separate units of the components (i) to (iii).

According to the invention the renin inhibitor (i) is selected from the group consisting of aliskiren, deliskiren, telikiren, and zankiren; (ii) the CCB is selected from the group consisting of amlodipine, felodipine, isradipine, lacidipine, nicardipine, nifedipine, niguldipine, niludipine, nimodipine, nisoldipine, nitrendipine, nivaldipine, ryosidine, anipamil, diltiazem, fendiline, flunarizine, gallopamil, mibefradil, prenylamine, tiapamil and verapamil; and the diuretic (iii) is selected from the group consisting of bumetanide, ethacrynic acid, furosemide, torsemide, amiloride, spironolactone, triamterene, chlorothalidone, chlorothiazide, hydrochlorothiazide, hydroflumethiazide, methylethiothiazide, metolazone, and dichlorphenamide and also amiloride. In each case where appropriate, e.g. if the compound is not present as a pharmaceutically acceptable salt per se as in the case of hydrochlorothiazide, these compounds also include their pharmaceutically acceptable salts.

The structure of the active agents identified by generic or tradenames may be taken from the actual edition of the standard compendium "The Merck Index" or from databases, e.g. LifeCycle Patents International (e.g. IMS World Publications). The corresponding content thereof is hereby incorporated by reference. Any person skilled in the art is fully enabled to identify the active agents and, based on these references, likewise enabled to manufacture and test the pharmaceutical indications and properties in standard test models, both in vitro and in vivo.

The present invention further relates to the above pharmaceutical composition for the treatment of heart failure such as (acute and chronic) congestive heart failure, left ventricular dysfunction and hypertrophic cardiomyopathy, diabetic cardiac myopathy, supraventricular and ventricular arrhythmias, atrial fibrillation, atrial flutter or detrimental vascular remodeling.

It can further be shown that combination therapy with the inventive combination and in particular with aliskiren, especially the hemi-fumarate salt thereof, amlodipine, especially the maleate or more preferably the besylate thereof, and hydrochlorthiazide (HCTZ) proves to be beneficial in the treatment and prevention of myocardial infarction and its sequelae. Such a combination therapy is also useful in treating atherosclerosis, angina (whether stable or unstable), and renal insufficiency (diabetic and non-diabetic). Furthermore, such a combination therapy can improve endothelial dysfunction, thereby providing benefit in diseases in which normal endothelial function is disrupted such as heart failure, angina pectoris and diabetes. Furthermore, the combination of the present invention may be used for the treatment or prevention of secondary aldosteronism, primary and secondary pulmonary hypertension, renal failure conditions, such as diabetic nephropathy, glomerulonephritis (including IgA nephropathy), renal fibrosis, scleroderma, glomerular sclerosis, proteinuria of renal disease, and also renal vascular hypertension, diabetic retinopathy, the management of other vascular disorders, such as migraine, peripheral vascular disease, Raynaud's disease, luminal hyperplasia, cognitive dysfunction (such as Alzheimer's), glaucoma and stroke, pulmonary and hepatic fibrosis, fibrotic diseases resulting from accumulation of excess extracellular matrix induced by TGF- β and proliferative diseases of smooth muscle cells (such as uterine fibroids).

The present invention furthermore relates to a method of treatment of a condition or a disease selected from the group consisting of hypertension, heart failure such as (acute and chronic) congestive heart failure, left ventricular dysfunction and hypertrophic cardiomyopathy, diabetic cardiac myopathy, supraventricular and ventricular arrhythmias, atrial fibrillation, atrial flutter, detrimental vascular remodeling, myocardial infarction and its sequelae, atherosclerosis, angina (whether unstable or stable), renal insufficiency (diabetic and non-diabetic), heart failure, angina pectoris, diabetes, secondary aldosteronism, primary and secondary pulmonary hypertension, renal failure conditions, such as diabetic nephropathy, glomerulonephritis (including IgA nephropathy), renal fibrosis, scleroderma, glomerular sclerosis, proteinuria of renal disease, and also renal vascular hypertension, diabetic retinopathy, the management of other vascular disorders, such as migraine, peripheral vascular disease, Raynaud's disease, luminal hyperplasia, cognitive dysfunction (such as Alzheimer's), glaucoma and stroke, pulmonary and hepatic fibrosis, fibrotic diseases resulting from accumulation of excess extracellular matrix induced by TGF, and proliferative diseases of smooth muscle cells, including uterine fibroids comprising

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administering a therapeutically effective amount of a combination of (i) a renin inhibitor, (ii) a CCB, and (iii) a diuretic or pharmaceutically acceptable salts thereof and a pharmaceutically acceptable carrier to a mammal in need of such treatment. Preferably, the renin inhibitor is aliskiren, the CCB is amlodipine, and the diuretic is HCTZ.

The invention likewise relates to the use of a combination of (i) a renin inhibitor, (ii) a CCB, and (iii) a diuretic, or pharmaceutically acceptable salts for the treatment of a disease or condition as described hereinbefore or hereinafter.

As used throughout the specification and in the claims, the term "treatment" embraces all the different forms or modes of treatment as known to those of the pertinent art and in particular includes preventive, curative and palliative treatment.

Diuretic activates the RAS, thus makes inhibition of RAS by renin inhibitor (RI) more effective. Addition of CCB to RI, whose activity is potentiated by diuretic, will lower e.g. blood pressure by a mechanism separate from RAS. CCB has been shown to be renoprotective at least in part through (i) inhibition of glomerular expression of TGF-beta & alpha-smooth muscle cell actin (Nephron 2000 Nov;86(3):315-26) and (ii) exerting growth-inhibitory activity through inhibiting multiple cell signal pathways (J Hypertens 2002 Jan;20(1):95-102).

Surprisingly it was found that using the inventive combination of divergent mechanisms maximizes the chance to avoid the activation of compensatory blood pressure regulating mechanisms that are stimulated with mono-therapy anti-hypertensive treatment. Unexpectedly, blocking the RAS is most effective when the system is activated. Thus, it is possible to achieve greater pharmacological inhibition of the RAS when blockers of this system are administered simultaneously with mild activators of the RAS. Such activation of the RAS can be accomplished with the calcium channel blockers and diuretics. In addition, each of these therapies alone is antihypertensive. The use of an RI in this combination provides the most effective and complete blockage of the RAS. The unexpected advantage of a triple vs dual combination is the (i) potentiated blood pressure lowering effect and (ii) more effective anti-proliferative effect through the combined actions of rennin inhibition (potentiated by diuretic) and CCB. Both of these activities are translated into enhanced tissue protection. The improved activity and benefit over dual combo results from a

potentiation or even synergistic interactions between 3 components. Furthermore, less side effects are can be manifested by the ability to use lower doses of the partners to be combined. For example, doses of individual components can be reduced by 2-7 fold or reduced by 3-7, 4-7, 5-7 or 6-7 fold, when given in combination and still achieve comparable blood pressure lowering activity compared to each individual agent. In humans, the superiority or surprising advantages of triple over dual combos can be demonstrated e.g. by testing of the combination for benefits on blood pressure lowering, left ventricular hypertrophy, renal protection (e.g., reversing, ameliorating, or delaying worsening of proteinuria; slowing decline in glomerular filtration rate or creatinine clearance, delay doubling of serum creatinine).

Prolonged and uncontrolled hypertensive vascular disease ultimately leads to a variety of pathological changes in target organs such as the heart and kidney. The presence of diabetes exacerbates these changes. Sustained hypertension can lead as well to an increased occurrence of stroke. Therefore, there is a strong need to evaluate the efficacy of antihypertensive therapy, an examination of additional cardiovascular endpoints, beyond those of blood pressure lowering, to get further insight into the benefits of combined treatment. The nature of hypertensive vascular diseases is multifactorial. Under certain circumstances, drugs with different mechanisms of action have been combined. However, simply using any combination of drugs having different modes of action does not necessarily lead to combinations with advantageous effects.

Potentiation is the enhancement of the biological effect of one agent by another agent to produce either an additive or greater than additive biological effect, compared to the effects from the individual agents, while synergism is the enhancement of the biological effect of one agent by another agent to produce a biological effect that is greater than that predicted by adding the effects of the individual components.

In one aspect the present invention relates to a pharmaceutical composition comprising (i) aliskiren, (ii) amlodipine, and (iii) hydrochlorothiazide (HCTZ) or pharmaceutically effective salts thereof.

In another embodiment the present invention relates to methods of treating cardiac and renal related conditions by administration of the pharmaceutical composition comprising (i)

aliskiren, especially the hemi-fumarate salt thereof, amlodipine, especially the maleate or more preferably the besylate thereof, and HCTZ.

The compounds to be combined can be present as pharmaceutically acceptable salts. If these compounds have, for example, at least one basic center, they can form acid addition salts. Corresponding acid addition salts can also be formed having, if desired, an additionally present basic center. The compounds having at least one acid group (for example COOH) can also form salts with bases. Corresponding internal salts may furthermore be formed, if a compound comprises e.g. both a carboxy and an amino group.

It has surprisingly been found that a combination of aliskiren, amlodipine, and HCTZ achieves greater therapeutic effect than the administration of each of these agents alone. Greater efficacy can also be documented as a prolonged duration of action. The duration of action can be monitored as either the time to return to baseline prior to the next dose or as the area under the curve (AUC) and is expressed as the product of the change in blood pressure in millimeters of mercury (change in mmHg) and the duration of the effect (minutes, hours or days).

Further benefits are that lower doses of the individual drugs to be combined according to the present invention can be used to reduce the dosage, for example, that the dosages need not only often be smaller but are also applied less frequently, or can be used to diminish the incidence of side effects. The combined administration of aliskiren, amlodipine, and HCTZ or pharmaceutically acceptable salts thereof results in a significant response in a greater percentage of treated patients, that is, a greater responder rate results, regardless of the underlying etiology of the condition. This is in accordance with the desires and requirements of the patients to be treated.

It can be shown that combination therapy with aliskiren, especially the hemi-fumarate salt thereof, amlodipine, especially the maleate or more preferably the besylate thereof, and HCTZ results in a more effective antihypertensive therapy (whether for malignant, essential, reno-vascular, diabetic, isolated systolic, or other secondary type of hypertension) through improved efficacy as well as a greater responder rate. The combination is also useful in the treatment or prevention of heart failure such as (acute and chronic) congestive heart failure, left ventricular dysfunction and hypertrophic cardiomyopathy, diabetic cardiac myopathy,

supraventricular and ventricular arrhythmias, atrial fibrillation, atrial flutter or detrimental vascular remodeling. It can further be shown that combination therapy with aliskiren, amlodipine, and HCTZ proves to be beneficial in the treatment and prevention of myocardial infarction and its sequelae. A combination therapy with aliskiren, amlodipine, and HCTZ is also useful in treating atherosclerosis, angina (whether stable or unstable), and renal insufficiency (diabetic and non-diabetic). Furthermore, combination therapy using aliskiren, amlodipine, and HCTZ can improve endothelial dysfunction, thereby providing benefit in diseases in which normal endothelial function is disrupted such as heart failure, angina pectoris and diabetes. Furthermore, the combination of the present invention may be used for the treatment or prevention of secondary aldosteronism, primary and secondary pulmonary hypertension, renal failure conditions, such as diabetic nephropathy, glomerulonephritis (including IgA nephropathy), renal fibrosis, scleroderma, glomerular sclerosis, proteinuria of renal disease, and also renal vascular hypertension, diabetic retinopathy, the management of other vascular disorders, such as migraine, peripheral vascular disease, Raynaud's disease, luminal hyperplasia, cognitive dysfunction (such as Alzheimer's), glaucoma and stroke, pulmonary and hepatic fibrosis, fibrotic diseases resulting from accumulation of excess extracellular matrix induced by TGF- β and proliferative diseases of smooth muscle cells (such as uterine fibroids).

The person skilled in the pertinent art is fully enabled to select a relevant test model to prove the efficacy of a combination of the present invention in the hereinbefore and hereinafter indicated therapeutic indications. Representative studies are carried out with a combination of aliskiren, especially the hemi-fumarate salt thereof, amlodipine, especially the maleate or more preferably the basylate thereof, and HCTZ applying the following methodology.

The advantages of the present combinations are, for example, demonstrated in a clinical study or in the test procedure as essentially described hereinafter. Many clinical study protocols adapted to test our combinations are known by the person skilled in the art. An example of a clinical trial useful to demonstrate the unexpected advantages of our new combinations is described by Nussberger J. et al. (Hypertension 2002 Jan;39(1):E1-8). The same protocol is performed with our preferred combinations such as described herein. This protocol is hereby incorporated into the present application by reference to this publications.

Drug efficacy is assessed in various animal models including those found below, using the following approximate dosages. Aliskiren is administered in subcutaneously implanted osmotic minipumps at approximately 1–200 mg/kg/day (monotherapy), and approximately 1–75 mg/kg/day (combination therapy). Amlodipine and HCTZ are administered orally in dosages below 75 mg/kg/day as mono- or combination therapy.

Among the animal models used to assess drug efficacy are the deoxycorticosterone acetate - salt rat (DOCA-salt) and the spontaneously hypertensive rat (SHR) models, either maintained on a normal salt diet or with salt loading (4-8% salt in rat chow or 1% NaCl as drinking water). The DOCA-salt test model utilizes either an acute or chronic study protocol. An acute study procedure involves assessment of the effects of various test substances over a six-hour experimental period using rats with indwelling femoral arterial and venous catheters. The Acute Study Procedure evaluates test substances for their ability to reduce blood pressure during the established phase of DOCA-salt hypertension. In contrast, the Chronic Study Procedure assesses the ability of test substances to prevent or delay the rise in blood pressure during the development phase of DOCA-salt hypertension. Therefore, blood pressure will be monitored in the chronic study procedure by means of a radiotransmitter. The radiotransmitter is surgically implanted into the abdominal aorta of rats, prior to the initiation of DOCA-salt treatment and thus, prior to the induction of hypertension. Blood pressure is chronically monitored for periods of up to 6 weeks (approximately one week prior to DOCA-salt administration and for 5 weeks thereafter).

Rats are anesthetized with 2-3% isoflurane in oxygen inhalant followed by Amytal sodium (amobarbital) 100 mg/kg, ip. The level of anesthesia is assessed by a steady rhythmic breathing pattern.

Acute study procedure:

Rats undergo a unilateral nephrectomy at the time of DOCA implantation. Hair is clipped on the left flank and the back of the neck and scrubbed with sterile alcohol swabs and povidone-iodine. During surgery rats are placed on a heating pad to maintain body temperature at 37 degrees C.

A 20 mm incision is made through the skin and underlying muscle to expose the left kidney. The kidney is freed of surrounding tissue, exteriorized and two ligatures (3-0 silk) are tied

securely around the renal artery and vein proximal to their juncture with the aorta. The renal artery and vein are then severed and the kidney removed. The muscle and skin wounds are closed with 4-0 silk suture and stainless steel wound clips, respectively. At the same time, a 15 mm incision is made on the back of the neck and a 3-week-release pellet (Innovative Research of America, Sarasota, Florida) containing deoxycorticosterone acetate (100 mg/kg) is implanted subcutaneously. The wound is then closed with stainless-steel clips and both wounds are treated with povidone/iodine; the rats are given a post-surgical intramuscular injection of procaine penicillin G (100,000 U) and buprenorphine (0.05 – 0.1 mg/kg) s.c. The rats are immediately placed on 1% NaCl + 0.2% KCl drinking water; this treatment continues for at least 3 weeks at which time the animals have become hypertensive and available for experimentation.

Forty-eight hours prior to experimentation, animals are anesthetized with isoflurane and catheters are implanted in the femoral artery and vein for measuring arterial pressure, collection of blood, and administration of test compounds. Rats are allowed to recover for 48 hours while tethered in a Plexiglas home cage which also serves as the experimental chamber.

Chronic study procedure:

This procedure is the same as above except that rats are implanted with a radiotransmitter, 7-10 days prior to the unilateral nephrectomy and initiation of DOCA and salt. In addition, rats do not undergo surgery for placement of femoral arterial and venous catheters. Radiotransmitters are implanted as described in M.K. Bazil, C. Krulan and R.L. Webb., Telemetric monitoring of cardiovascular parameters in conscious spontaneously hypertensive rats, J Cardiovasc. Pharmacol. 21: 897-905, 1993.

Protocols are then set-up on the computer for measurement of blood pressure, heart rate, etc, at predetermined time points. Baseline data are collected at various time points and over various time intervals. For example, baseline or pre-dose values usually consist of data collection and averaging over 3 consecutive, 24-hour time periods prior to drug administration.

Blood pressure, heart rate and activity are determined at various pre-selected time points before, during, and after drug administration. All measurements are performed in

unrestrained and undisturbed animals. The maximum study time, determined by battery life, could be as long as nine months.

Additionally, SHR are utilized to study the effects of aliskiren in combination with amlodipine and HCTZ. The hypertensive background of the SHR is modified either by chronic salt loading in an effort to suppress the renin-angiotensin system (RAS) or chronic salt depletion to activate the RAS in the SHR. These manipulations will be carried out to more extensively evaluate the efficacy of the various test substances. For experiments performed in spontaneously hypertensive rats (SHR), these animals are supplied by Taconic Farms, Germantown, New York (Tacon(SHR)IBR). A radiotelemetric device (Data Sciences International, Inc., St. Paul, Minnesota) is implanted into the lower abdominal aorta of all test animals between the ages of 14 to 16 weeks of age. All SHR are allowed to recover from the surgical implantation procedure for at least 2 weeks prior to the initiation of the experiments. Cardiovascular parameters are continuously monitored via the radiotransmitter and transmitted to a receiver where the digitized signal is then collected and stored using a computerized data acquisition system. Blood pressure (mean arterial, systolic and diastolic pressure) and heart rate are monitored in conscious, freely moving and undisturbed SHR in their home cages. The arterial blood pressure and heart rate are measured every 10 minutes for 10 seconds and recorded. Data reported for each rat represent the mean values averaged over a 24 hour period and are made up of the 144-10 minute samples collected each day. The baseline values for blood pressure and heart rate consist of the average of three consecutive 24 hour readings taken prior to initiating the drug treatments. All rats are individually housed in a temperature and humidity controlled room and are maintained on a 12 hour light/dark cycle.

In addition to the cardiovascular parameters, weekly determinations of body weight also are recorded in all rats. Treatments are administered in the drinking water, via daily oral gavage or in osmotic minipumps as stated above. If given in drinking water, water consumption is measured five times per week. Doses of drugs for individual rats are then calculated based on water consumption for each rat, the concentration of drug substance in the drinking water, and individual body weights. All drug solutions in the drinking water are made up fresh every three to four days.

Upon completion of the chronic studies, SHR or DOCA-salt rats are anesthetized and the heart rapidly removed. After separation and removal of the atrial appendages, left ventricle and left plus right ventricle (total) are weighed and recorded. Left ventricular and total ventricular mass are then normalized to body weight and reported. All values reported for blood pressure and cardiac mass represent the group mean $\pm$ sem.

Vascular function and structure are evaluated after treatment to assess the beneficial effects of the combination. SHR are studied according to the methods described by Intengan HD, Thibault S, Li JS, Schiffrin EL, Circulation 1999, 100 (22): 2267-2275. Similarly, the methodology for assessing vascular function in DOCA-salt rats is described in Intengan HD, Park JB, Schiffrin, EL, Hypertension, 1999, 34 (4 Part 2): 907-913.

Drug efficacy for inhibiting diabetic renal disease is assessed in various animal models including spontaneously diabetic (db/db) mice (Ziyadeh F, Hoffman B, Han D, Iglesias-de la Cruz M, Hong S, Isoro M, Chen S, McGowan F, Sharma K. Long-term prevention of renal insufficiency, excess matrix gene expression, and glomerular mesangial matrix expansion by treatment with monoclonal antitransforming growth factor- β antibody in db/db diabetic mice. Proc Natl Acad Sci. 2000; 97:8015-8020). The db/db mouse is a widely used model for the renal glomerular lesions seen in non-insulin dependent diabetes (type 2 diabetes). Mice are treated daily with vehicle, monotherapy or combination therapy. Every 2 weeks throughout the study urine is collected to measure urinary albumin excretion. At the end of the experiment blood is collected for determining plasma creatinine levels. The kidneys are preserved *in situ* by perfusion fixation, they are removed and renal pathology is assessed quantitatively by light microscopy and image analysis. Drug efficacy is defined by the reduction (vs vehicle controls) of (i) urinary albumin excretion, (ii) plasma creatinine, and by (iii) the inhibition of renal glomerulosclerosis.

Drug efficacy for inhibiting renal fibrosis is assessed in various animal models including the unilateral ureter obstruction model in rats (Isnikloya, S; Morrissey, J; McCracken, R; Reyes, A; Klahr, S. Angiotensin II receptor antagonist ameliorates renal tubulointerstitial fibrosis caused by unilateral ureteral obstruction. Kid Int. 47:1285-1294, 1995). This model involves ligating one ureter, which results in renal fibrosis by 5 days in the kidney drained by that ureter. Drug efficacy is assessed by quantifying with light microscopy and image analysis, the extent of renal fibrosis among treated groups. ACE inhibitors and AT1 receptor blockers

inhibit renal fibrosis in this model (Klar, S; Ishikawa, S; Morrissey, J. Role of angiotensin II in the tubulointerstitial fibrosis of obstructive nephropathy. *Amer J Kid Dis.* 26:141-146, 1995). It can therefore be demonstrated that combination therapy with aliskiren, amlodipine, and HCTZ provides increased protection vs monotherapy.

A therapeutically effective amount of each of the components of the combination of the present invention may be administered separately, simultaneously or sequentially and in any order. The unit dose form may also be a fixed combination.

The corresponding active ingredient or a pharmaceutically acceptable salt thereof may also be used in form of a hydrate or include other solvents used for crystallization.

The pharmaceutical compositions according to the invention can be prepared in a manner known per se and are those suitable for enteral, such as oral or rectal, and parenteral administration to mammals (warm-blooded animals), including man, comprising a therapeutically effective amount of the pharmacologically active compound, alone or in combination with one or more pharmaceutically acceptable carriers, especially suitable for enteral or parenteral application. Typical oral formulations include tablets, capsules, syrups, elixirs and suspensions. Typical injectable formulations include solutions and suspensions.

The invention also relates to combining separate pharmaceutical compositions in kit form. That is a kit combining two or three separate units, e.g. an aliskiren pharmaceutical composition, an amlodipine pharmaceutical composition, and an HCTZ pharmaceutical composition, or in case of two separate units a kit combining a pharmaceutical composition of two of the active agents and a pharmaceutical composition of the remaining active ingredient. The kit form is particularly advantageous when the separate components must be administered in different dosage forms (e.g. parenteral aliskiren formulation and oral amlodipine and HCTZ formulations) or are administered at different dosage intervals.

In a preferred embodiment, the (commercial) product is a commercial package comprising as active ingredients the combination according to the present invention (in the form of two or three separate units of the components (i) to (iii)), together with instructions for its simultaneous, separate or sequential use, or any combination thereof, in the delay of progression or treatment of the diseases mentioned herein.

These pharmaceutical preparations are for enteral, such as oral, and also rectal or parenteral, administration to homeotherms, with the preparations comprising the pharmacological active compound either alone or together with customary pharmaceutical auxiliary substances. For example, the pharmaceutical preparations consist of from about 0.1 % to 90 % preferably of from about 1 % to about 80 %, of the active compounds. Pharmaceutical preparations for enteral or parenteral administration are, for example, in unit dose forms, such as coated tablets, tablets, capsules or suppositories and also ampoules. These are prepared in a manner which is known per se, for example using conventional mixing, granulation, coating, solutionizing or lyophilizing processes. Thus, pharmaceutical preparations for oral use can be obtained by combining the active compounds with solid excipients, if desired granulating a mixture which has been obtained, and, if required or necessary, processing the mixture or granulate into tablets or coated tablet cores after having added suitable auxiliary substances.

The dosage of the active compound can depend on a variety of factors, such as mode of administration, homeothermic species, age and/or individual condition.

Preferred dosages for the active ingredients of the pharmaceutical combination according to the present invention are therapeutically effective dosages, especially those which are commercially available.

Aliskiren is supplied in the form of suitable dosage unit form, for example, a capsule or tablet, and comprising a therapeutically effective amount, e.g. from about 1 to about 1,000 mg, preferably from about 150 to about 500 mg, of aliskiren which may be applied to patients. Preferably, aliskiren is applied once a day.

In case of amlodipine, preferred dosage unit forms are, for example, tablets or capsules comprising e.g. from about 1 mg to about 40 mg, preferably 2.5 to 20 mg daily when administered orally. In case of HCTZ, preferred dosage unit forms are, for example, tablets or capsules comprising e.g. from about 5 mg to about 200 mg, preferably from about 5 mg to about 25 mg, administered orally once a day. The above doses encompass a therapeutically effective amount of the active ingredients of the present invention.

An example of a preferred composition comprises an amount of Aliskiren between 140 and 220 mg e.g. 180 mg, an amount of amlodipine between 2 and 12 mg (e.g. 2.5 or 5 or 10 mg) and an amount of HCTZ between 5 and 30 mg, preferably between 5 and 15 (e.g. 12.5 or 6.25 mg).

Another example of a preferred composition comprises an amount of Aliskiren between 350 and 550 mg e.g. 450 mg, an amount of amlodipine between 2 and 12 mg (e.g. 2.5 or 5 or 10 mg) and an amount of HCTZ between 5 and 30 mg preferably between 10 and 30 (e.g. 12.5 mg or 25 mg).

Another example of a preferred composition comprises an amount of Aliskiren between 550 and 700 mg e.g. 640 mg, an amount of amlodipine between 2 and 12 mg (e.g. 2.5 or 5 or 10 mg) and an amount of HCTZ between 5 and 30 mg preferably between 10 and 30 (e.g. 12.5 mg or 25 mg).

failure, angina pectoris, diabetes, secondary aldosteronism, primary and secondary pulmonary hypertension, renal failure conditions, such as diabetic nephropathy, glomerulonephritis (including IgA nephropathy), renal fibrosis, scleroderma, glomerular sclerosis, proteinuria of renal disease, and also renal vascular hypertension, diabetic retinopathy, the management of other vascular disorders, such as migraine, peripheral vascular disease, Raynaud's disease, luminal hyperplasia, cognitive dysfunction (such as Alzheimer's), glaucoma and stroke, pulmonary and hepatic fibrosis, fibrotic diseases resulting from accumulation of excess extracellular matrix induced by TGF, and proliferative diseases of smooth muscle cells, including uterine fibroids comprising administering a therapeutically effective amount of a pharmaceutical composition according to any one of claims 1 to 4 to a mammal in need of such treatment.

7. The use of a combination according to any one of claims 1 to 5 for the manufacture of a medicament for the treatment of a condition or a disease selected from the group consisting of hypertension, heart failure such as (acute and chronic) congestive heart failure, left ventricular dysfunction and hypertrophic cardiomyopathy, diabetic cardiac myopathy, supra-ventricular and ventricular arrhythmias, atrial fibrillation, atrial flutter, detrimental vascular remodeling, myocardial infarction and its sequelae, atherosclerosis, angina (whether unstable or stable), renal insufficiency (diabetic and non-diabetic), renal failure, angina pectoris, diabetes, secondary aldosteronism, primary and secondary pulmonary hypertension, renal failure conditions, such as diabetic nephropathy, glomerulonephritis (including IgA nephropathy), renal fibrosis, scleroderma, glomerular sclerosis, proteinuria of renal disease, and also renal vascular hypertension, diabetic retinopathy, the management of other vascular disorders, such as migraine, peripheral vascular disease, Raynaud's disease, luminal hyperplasia, cognitive dysfunction (such as Alzheimer's), glaucoma and stroke, pulmonary and hepatic fibrosis, fibrotic diseases resulting from accumulation of excess extracellular matrix induced by TGF, and proliferative diseases of smooth muscle cells, including uterine fibroids.
8. The use of a combination according to any one of claims 1 to 5 for the treatment of a condition or a disease selected from the group consisting of hypertension, heart failure such as (acute and chronic) congestive heart failure, left ventricular dysfunction and hypertrophic cardiomyopathy, diabetic cardiac myopathy, supra-ventricular and

ventricular arrhythmias, atrial fibrillation, atrial flutter, detrimental vascular remodeling, myocardial infarction and its sequelae, atherosclerosis, angina (whether unstable or stable), renal insufficiency (diabetic and non-diabetic), heart failure, angina pectoris, diabetes, secondary aldosteronism, primary and secondary pulmonary hypertension, renal failure conditions, such as diabetic nephropathy, glomerulonephritis (including IgA nephropathy), renal fibrosis, scleroderma, glomerular sclerosis, proteinuria of renal disease, and also renal vascular hypertension, diabetic retinopathy, the management of other vascular disorders, such as migraine, peripheral vascular disease, Raynaud's disease, luminal hyperplasia, cognitive dysfunction (such as Alzheimer's), glaucoma and stroke, pulmonary and hepatic fibrosis, fibrotic diseases resulting from accumulation of excess extracellular matrix induced by TGF, and proliferative diseases of smooth muscle cells, including uterine.

9. A commercial package comprising

- (i) a renin inhibitor or a pharmaceutically acceptable salt thereof,
- (ii) a calcium channel blocker (CCB) or a pharmaceutically acceptable salt thereof,
- and

- (iii) a diuretic or a pharmaceutically acceptable salt thereof,

in the form of two or three separate units of the components (i) to (iii),

together with instructions for simultaneous, separate or sequential use thereof in the delay of progression or treatment of a condition or disease selected from the group consisting of hypertension, heart failure such as (acute and chronic) congestive heart failure, left ventricular dysfunction and hypertrophic cardiomyopathy, diabetic cardiac myopathy, supraventricular and ventricular arrhythmias, atrial fibrillation, atrial flutter, detrimental vascular remodeling, myocardial infarction and its sequelae, atherosclerosis, angina (whether unstable or stable), renal insufficiency (diabetic and non-diabetic), heart failure, angina pectoris, diabetes, secondary aldosteronism, primary and secondary pulmonary hypertension, renal failure conditions, such as diabetic nephropathy, glomerulonephritis (including IgA nephropathy), renal fibrosis, scleroderma, glomerular sclerosis, proteinuria of renal disease, and also renal vascular hypertension, diabetic retinopathy, the management of other vascular disorders, such as migraine, peripheral vascular disease, Raynaud's disease, luminal hyperplasia, cognitive dysfunction (such as Alzheimer's), glaucoma and stroke, pulmonary and hepatic fibrosis, fibrotic diseases resulting from accumulation of excess extracellular

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matrix induced by TGF β and proliferative diseases of smooth muscle cells, including uterine.

10. A commercial package according to claim 9, wherein the renin inhibitor (i) is aliskiren, the CCB (ii) is amlodipine and the diuretic (iii) is hydrochlorothiazide.
11. A kit of parts comprising
 - (i) a pharmaceutical composition of a renin inhibitor,
 - (ii) a pharmaceutical composition of a calcium channel blocker (CCB), and
 - (iii) a pharmaceutical composition of a diuretic
 in the form of two or three separate units of the components (i) to (iii).
12. A kit of parts according to claim 11, wherein the renin inhibitor (i) is selected from the group consisting of aliskiren, deliskiren, belakiren, and zankiren; the CCB (ii) is selected from the group consisting of amlodipine, felodipine, isradipine, lacidipine, nicardipine, nifedipine, niguldipine, niludipine, nimodipine, nisoldipine, nitrendipine, nivaldipine, rycosidine, amlodipine, diltiazem, fendiline, flunarizine, gallopamil, mibefradil, prenylamine, flaperid and verapamil; and the diuretic (iii) is selected from the group consisting of bumetanide, ethacrynic acid, furosemide, torsemide, amiloride, spironolactone, triamterene, enoxithiazone, chlorothiazide, hydrochlorothiazide, hydroflumthiazide, methychlorothiazide, metolazone, and dichlorphenamide.
13. A kit of parts according to claim 11, wherein the renin inhibitor (i) is aliskiren, the CCB (ii) is amlodipine, and the diuretic (iii) is hydrochlorothiazide.
14. A kit of parts according to claim 11, wherein aliskiren in an amount in the range from 1 to 1,000 mg, amlodipine in an amount in the range from 1 to 40 mg, and hydrochlorothiazide in an amount in the range from 5 to 200 mg.
15. A kit of parts according to claim 11, wherein aliskiren in an amount in the range from 140 to 550 mg, amlodipine in an amount in the range from 2 to 12 mg, and hydrochlorothiazide in an amount in the range from 5 to 30 mg.

INTERNATIONAL SEARCH REPORT

PCT/EP 03/05188

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K45/56 A61P4/00

According to International Patent Classification (IPC) to international classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A61K

Documentation searched (classification system followed by classification symbols) documents are included in the fields searched

Electronic data has been searched (name of data base and, where practical, search terms used)

EPO-Internal, PAI, ATIP, A, BIOSIS, EMBASE, CHEM ABS Data

C. DOCUMENTS CONSIDERED OF RELEVANCE

Category *	Citation of document (classification of document appropriate of the relevant passages)	Relevant to claim No.
P, X	WO 02 43867 A (NOVARTIS-ERFINDUNG.N) 20 May 2002 (WO) 35-20 claims 1-6, 7 page 21 paragraph 2	1-15
P, X	WO 02 43867 A (NOVARTIS-ERFINDUNG.N) 6 June 2002 (WO) 35-20 claims 1-8, 11, 12, 14, 16, 17 page 11 paragraph 1 page 12 paragraph 1	1-8
A	WO 02 43867 A (NOVARTIS-ERFINDUNG.N) 25 June 2002 (WO) 35-20 claims 1-17	1

☐ Further documents are listed in the annex.

☒ Patent family members are listed in annex.

* Special categories of cited documents

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document published prior to the international filing date
- *L* document which is a translation of a document (patent or otherwise) or which is otherwise made available to the public by means of citation or otherwise already published
- *O* document relevant to the invention but not available by other means
- *P* document published after the international filing date but later than the priority date

later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

P document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

document member of the same patent family

Date of the actual filing of the international application

14 August 2000

Date of mailing of the international search report

21/08/2003

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INTERNATIONAL SEARCH REPORT

PCT/EP 03/05188

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: —
because they relate to subject matter not required to be searched by this Authority, namely:
see FURTHER INFORMATION sheet PCT/ISA/210
2. ☒ Claims Nos.: —
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210
3. ☐ Claims Nos.: —
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this International Application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without incurring an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically: claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTAINED FROM PCTASA/ 10

Continuation of Box 1.1

Although claim 6 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

Continuation of Box 1.1

Rule 39.1(iv) PCT - Methods for treatment of the human or animal body by therapy

Continuation of Box 1.2

Present claims 1,6-8, 11 relate to a product/compound/method/apparatus defined by reference to a desirable characteristic or property, namely:

- 1) "Renin inhibitor"
- 2) "Calcium channel blocker"
- 3) "Diuretic"

The claims cover all products/compounds, methods/apparatus having this characteristic or property, whereas the application provides support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT for only a very limited number of such products/compounds/methods/apparatus. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Independent of the above reasoning, the claims also lack clarity (Article 6 PCT). An attempt is made to define the product/compound/method/apparatus by reference to a result to be achieved. Again, this lack of clarity in the present case is such as to render a meaningful search over the whole of the claimed scope impossible. Consequently, the search has been carried out for those parts of the claims which appear to be clear, supported and disclosed, namely, the compounds specified in claims 2-5,10,13-15, with due regard to the generic idea underlying the present application.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination of matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

Information on patent family members

PCT/EP 03/05188

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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		CA 2428647 A1	23-05-2002
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US 20050271720A1

(19) **United States**
(12) **Patent Application Publication** (10) **Pub. No.: US 2005/0271720 A1**
Kolatkhar et al. (43) **Pub. Date: Dec. 8, 2005**

(54) **PHARMACEUTICAL COMPOSITION
CONTAINING IRBESARTAN**

Publication Classification

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(51) **Int. Cl.⁷** **A61K 31/4184; A61K 9/20**
(52) **U.S. Cl.** **424/464; 514/381**

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(57) **ABSTRACT**

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(21) Appl. No.: **11/143,556**

(22) Filed: **Jun. 2, 2005**

Related U.S. Application Data

(60) Provisional application No. 60/577,427, filed on Jun.
4, 2004.

This invention relates to pharmaceutical compositions containing irbesartan, providing oral formulations with a high relative amount or concentration of irbesartan. In one embodiment, the present invention provides an oral formulation of irbesartan containing greater than 70% w/w irbesartan. In another embodiment, the invention provides an oral formulation of irbesartan which exhibits a dissolution profile according to which greater than about 85% of the irbesartan is dissolved within about 30 minutes using USP apparatus 2, placing the tablet in 1000 mL of 0.1N hydrochloric acid at 37° C. with paddle speed of 50 rpm. The formulation can optionally contain at least one additional active ingredient.

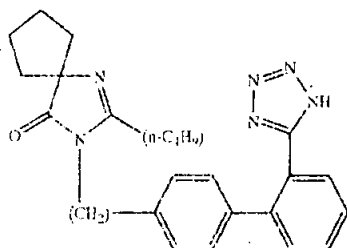
PHARMACEUTICAL COMPOSITION CONTAINING IRBESARTAN

FIELD OF THE INVENTION

[0001] This application relates to pharmaceutical compositions containing irbesartan, and to pharmaceutical compositions containing irbesartan and hydrochlorothiazide.

BACKGROUND OF THE INVENTION

[0002] Irbesartan is chemically described as 2-butyl-3-[[29-(1H-tetrazol-5-yl)-[1,19-biphenyl]-4-yl]methyl]-1,3-diazaspiro[4,4]non-1-en-4-one, also as 2-n-butyl-4-spiro[cyclopentane-1-yl]-(2'-(tetrazol-5-yl)biphenyl-4-yl)methyl]-2-imidazol-5-one, also as 2-butyl-3-[[2'-(1H-tetrazol-5-yl)-[1,1'-biphenyl]-4-yl]methyl]-1,3-diazaspiro[4,4]non-1-en-4-one. Its empirical formula is $C_{28}H_{29}N_5O$, and it has the following structure:



[0003] Irbesartan has a molecular weight of 428.5. The compound is described in U.S. Pat. No. 5,270,317, which is incorporated herein in its entirety.

[0004] In the United States, irbesartan is available for oral administration tablets containing 75 mg, 150 mg, or 300 mg of irbesartan, which are sold under the trade name AVAPRO. The drug also is formulated as 150 and 300 mg tablets that also include 12.5 mg hydrochlorothiazide, which are sold under the trade name AVALIDE.

[0005] As noted in U.S. Pat. No. 6,342,247, irbesartan is a fluffy material with relatively low bulk, and tap densities. In addition, irbesartan has certain undesirable flow characteristics. These properties make it difficult to formulate a large amount of the drug into a small tablet. Indeed, the '247 patent describes an oral formulation of irbesartan containing only up to 70% of the drug. Accordingly, there is a need for an improved formulation of irbesartan that contains a higher amount of the active ingredient.

SUMMARY OF THE INVENTION

[0006] This invention relates to pharmaceutical compositions comprising irbesartan, providing oral formulations with a high relative amount or concentration of irbesartan. In one embodiment, the present invention provides an oral formulation of irbesartan containing greater than 70% w/w irbesartan. In another embodiment, the invention provides an oral formulation of irbesartan which exhibits a dissolution profile according to which greater than about 85% of the irbesartan is dissolved within about 30 minutes, preferably greater than about 80% of the irbesartan is dissolved within about 10 minutes, using USP apparatus 2, placing the tablet in 1000 mL of 0.1 N hydrochloric acid at 37° C. with paddle

speed of 50 rpm. In another embodiment, the invention provides an oral formulation of two active pharmaceutical agents, irbesartan, and a diuretic, such as hydrochlorothiazide. These aspects and advantages, as well as additional inventive features, will be apparent upon reading the following detailed description. The formulations can optionally contain at least one additional active ingredient.

DETAILED DESCRIPTION OF THE INVENTION

[0007] The invention provides an oral formulation comprising irbesartan, and it provides an oral composition comprising irbesartan and hydrochlorothiazide. The irbesartan for inclusion in the inventive formulation can be manufactured according to any desired method, many of which are known to those of ordinary skill in the art. Examples of suitable methods to manufacture irbesartan are described in U.S. Pat. No. 5,270,317, which is incorporated herein in its entirety. Hydrochlorothiazide is also well known and can be manufactured by methods known in the art.

[0008] In one embodiment, the invention provides an oral formulation comprising irbesartan that includes at least about 70% irbesartan w/w. Preferably, the formulation includes at least about 75% w/w irbesartan, and more preferably the formulation includes from about 75% w/w to about 80% w/w irbesartan. A higher relative amount or concentration of irbesartan can be included, if desired.

[0009] In another embodiment, the invention provides an oral formulation comprising irbesartan which exhibits an improved dissolution profile according to the U.S. Pharmacopeia, using USP apparatus 2, placing the tablet in 1000 mL of 0.1N hydrochloric acid at 37° C. with paddle speed of 50 rpm. In some embodiments of the invention, the oral formulation comprising irbesartan exhibits a dissolution profile according to which greater than about 80% of the irbesartan is dissolved within about 10 minutes, and even more preferably greater than about 85% of the irbesartan is dissolved within about 10 minutes. The present invention provides, in another aspect, an oral formulation comprising irbesartan which exhibits a dissolution profile according to which at least about 75% of the irbesartan is dissolved within about 5 minutes, at least about 85% of the irbesartan is dissolved within about 10 minutes and at least about 95% of the irbesartan is dissolved in about 20 minutes. In accordance with another aspect of the invention, an oral formulation comprising irbesartan is provided which exhibits a dissolution profile according to which at least 97% of irbesartan is dissolved within 30 minutes. In some embodiments of the invention, the oral formulation comprising irbesartan exhibits a dissolution profile according to which greater than about 85% of the irbesartan is dissolved within about 30 minutes.

[0010] In addition to irbesartan, the oral formulation can include at least one additional active agent or combination of additional active agents. A preferred active agent to include in the formulation is a diuretic agent, such as hydrochlorothiazide, bendroflumethiazide, benzthiazide, chlorothiazide, chlorthalidone, cyclothiazide, hydroflumethiazide, methyclothiazide, metolazone, polythiazide, quinethazone, and trichlormethiazide. Preferably, at least one diuretic is a thiazide such as chlorothiazide and hydrochlorothiazide.

Hydrochlorothiazide, the 3,4-dihydro derivative of chlorothiazide, is the preferred diuretic for inclusion in the inventive composition. Its chemical name is 6-chloro-3,4-dihydro-2H-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide. Its empirical formula is $C_7H_8ClN_3O_4S_2$. Hydrochlorothiazide can be prepared by methods known to those of skill in the art. The amount of diuretic, such as hydrochlorothiazide is included in the formulation can be varied to achieve the desired therapeutic effect. In a preferred embodiment, the amount of diuretic is from about 3% to about 7% by weight of the formulation, more preferably, 3.32 to about 6.65% by weight of the formulation. The preferred diuretic is hydrochlorothiazide.

[0011] In addition to irbesartan and optional additional active ingredient or combination of additional active ingredients, the formulation contains at least one pharmaceutically acceptable excipient. In this context, the term "excipient" refers to pharmaceutically acceptable chemicals known to those of ordinary skill in the art of pharmacy to aid the administration of the medicinal agent. Preferable excipients for inclusion in the inventive formulation include binders, surfactants, diluents, disintegrants, antiadherents, and lubricants.

[0012] Preferably, the inventive composition comprises, one or more binders. Suitable "binders" can be selected from those capable of facilitating granulation of the irbesartan into larger, denser, and more free-flowing particles. Preferred binders include povidone (most preferably employed in the range of 1.0-7.0% by weight), pregelatinized starch (most preferably employed in the range of 1.0-10.0% by weight), alginate acid (most preferably employed in the range of 1.0-7.0% by weight) or sodium alginate (most preferably employed in the range of 1.0-5.0% by weight), cellulose or cellulose derivatives such as carboxymethylcellulose sodium (most preferably employed in the range of 1.0-6.0% by weight), ethylcellulose (most preferably employed in the range of 1.0-4.0% by weight), hydroxyethyl cellulose (most preferably employed in the range of 1.0-5.0% by weight), hydroxypropyl cellulose (most preferably employed in the range of 1.0-7.0% by weight), hydroxypropyl methylcellulose (most preferably employed in the range of 1.0-6.0% by weight) or methylcellulose (most preferably employed in the range of 1.0-6.0% by weight), gelatin (most preferably employed in the range of 1.0-7.0% by weight). Other binders known to those of skill in the art can be employed. Preferably, the binder is povidone, most preferably, PVP K-30, and, where present, it can represent of from about 2.0% w/w to about 2.15% w/w, most preferably 2.13% w/w, of the formulation. Another preferred binder is pregelatinized starch, most preferably, starch 1500 and, where present, the pregelatinized starch (starch 1500) typically represents from about 6.35%, most preferably, 6.38% w/w, and about 8.0% w/w of the formulation.

[0013] The inventive composition preferably includes at least one disintegrant. Suitable "disintegrants" can be selected from one or more components, which facilitate the break up of a tablet prepared from the composition when placed in contact with an aqueous medium. Any suitable disintegrant can be employed within the inventive formulation. Preferred disintegrant are croscarmellose sodium, such as Ac-Di-Sol (most preferably employed in the range of 1.0-7.0% by weight), alginate acid (most preferably employed in the range of 1.0-7.0% by weight) or sodium alginate (most preferably employed in the range of 1.0-7.0% by weight), carboxymethylcellulose sodium (most preferably employed in the range of 1.0-7.0% by weight),

crospovidone (most preferably employed in the range of 1.0-7.0% by weight), sodium starch glycolate (most preferably employed in the range of 1.0-7.0% by weight), pregelatinized starch (most preferably employed in the range of 1.0-7.0% by weight). Where present, typically croscarmellose. Where present, preferably, croscarmellose sodium (Ac-Di-Sol) represents from about 3.15%, preferably 3.19%, w/w to about 5.0%, preferably 4.0%, w/w of the formulation.

[0014] The inventive composition preferably includes at least one surfactant. Suitable "surfactants" include compounds which aid in wetting so as to enhance dissolution. Any suitable surfactant can be employed in the inventive formulation. Preferred surfactants are sodium lauryl sulfate (most preferably employed in the range of 0.2-6.0% by weight), poly(oxyethylene), poly(oxypropylene) block copolymers such as poloxamers, especially Poloxamer 188 (most preferably employed in the range of 0.2-6.0% by weight). Where present, the Poloxamer 188 typically represents from about 1.00%, preferably 1.06%, w/w to about 2.0% w/w of the formulation.

[0015] The formulation preferably includes one or more diluents. Suitable "diluents" include compounds which are capable of providing bulk to obtain a desired mass, such as desired tablet mass. Any suitable diluent can be employed in the inventive formulation. Preferred diluents are microcrystalline cellulose, such as Avicel PH 102 FMC, inorganic phosphates such as dibasic calcium phosphate, sugars such as lactose hydrous or lactose anhydrous and mannitol. Diluents are preferably included in the range of 2-10% by weight of the formulation. Where present, the microcrystalline cellulose typically represents from about 1% w/w to about 7.5% w/w of the formulation. For formulations that include only irbesartan as the active pharmaceutical agent, microcrystalline cellulose, where present, typically represents from about 1.9% w/w, to about 7.5% w/w of the formulation. For formulations which include irbesartan and diuretics, such as hydrochlorothiazide, as the active pharmaceutical agents, microcrystalline cellulose, when present, typically represents from about 1.9% w/w to about 6% w/w of the formulation. In some embodiments of the invention, microcrystalline cellulose, preferably is present in an amount of from about 1.97% w/w to about 5.3% w/w of the formulation, preferably 5.29% w/w. In other embodiments, microcrystalline cellulose preferably is present in an amount of from about 3.56% w/w to about 5.96% w/w of the formulation.

[0016] The inventive composition can further include at least one antiadherent. Suitable "antiadherents" include compounds that contribute to the flowability of the formulation. Any suitable antiadherents can be employed in the inventive formulation. Preferred antiadherents are silicon dioxide, such as Syloid 244 (most preferably employed in the range of 0.2-2.0% by weight) or talc (most preferably employed in the range of 0.5-5.0% by weight). Where present, the silicon dioxide typically represents from about 0.4% w/w to about 0.5% w/w of the formulation.

[0017] The composition of the present invention preferably includes at least one lubricant. Suitable "lubricants" include compounds that assist in preparing the desired form of the formulation for administration, such as tableting. Any suitable lubricant can be employed in the inventive formulation. Preferred lubricants are fatty acids or fatty acid derivatives such as calcium stearate (most preferably employed in the range of 0.5-2.0% by weight), glyceryl

monostearate (most preferably employed in the range of 0.5-2.0% by weight); glyceryl palmitostearate (most preferably employed in the range of 0.5-2.0% by weight); magnesium stearate (most preferably employed in the range of 0.2-2.0% by weight); sodium lauryl sulfate (most preferably employed in the range of 0.5-2.0% by weight); sodium stearyl fumarate (most preferably employed in the range of 0.5-2.0% by weight); zinc stearate; stearic acid (most preferably employed in the range of 0.5-3.0% by weight); hydrogenated vegetable oil (most preferably employed in the range of 0.5-5.0% by weight); polyalkylene glycols such as polyethylene glycol (most preferably employed in the range of 1.0-5.0% by weight); talc (most preferably employed in the range of 1.0-5.0% by weight). Where present, the magnesium stearate represents from about 1.0% w/w to about 1.1% w/w of the formulation, preferably from about 1.0% w/w to about 1.06% w/w of the formulation.

[0018] Preferred compositions according to the invention is set forth in Table 1:

TABLE 1

Preferred Ingredients	Component	Concentration Range (% w/w)
Irbesartan	Active drug	75-79.79
Pregelatinized starch (starch 1501)	Binder	6.38-8.0
Povidone (PVP K-30)	Binder	2-2.13
Poloxamer 188	Surfactant	1.06-2.0
Microcrystalline Cellulose (Avicel PH 102)	Diluent	5.06-7.5
Croscarmellose Sodium (Ac-Di-Sol)	Disintegrant	3.49-4.0
Silicon Dioxide (syloid 244)	Antiadherent	0.43-0.5
Magnesium Stearate	Lubricant	1.0-1.06

[0019] The inventive formulation includes any form of irbesartan for oral administration, or any form of irbesartan and diuretic, such as hydrochlorothiazide, such as a tablet, caplet, capsule or the like. The preferred formulation is a tablet. Most preferably, tablets of the present invention contain (per tablet) 300 mg of irbesartan. The total weight of the tablet preferably is between 376 mg and 400 mg.

[0020] Formulations containing irbesartan can be prepared by any suitable method. A preferred method for forming a tablet formulation comprising irbesartan according to one embodiment of the present invention is by a wet granulation process. By way of example, the irbesartan formulation can be prepared according to the following method:

- [0021] 1. Irbesartan is partially granulated with granulating solution of povidone in purified water using high shear mixer.
- [0022] 2. Pregelatinized starch is mixed with the mixture of step 1 in high shear mixer.
- [0023] 3. The blend of step 2 is granulated with a granulating solution of Poloxamer 188 in purified water using high shear mixer.
- [0024] 4. The granules formed in step 3 are dried in fluid bed dryer.
- [0025] 5. The dried granules are sized by passing them through an oscillating granulator.
- [0026] 6. The milled dried granulate of step 5 is mixed with microcrystalline cellulose, croscarmellose sodium and silicon dioxide in a blender.

[0027] 7. Magnesium stearate is added to the mixture of step 6 and mixed.

[0028] 8. The mixture from step 7 is compressed to form tablets using a tablet press.

[0029] Formulations that include irbesartan and a diuretic, such as hydrochlorothiazide, can include binders such as povidone, without a surfactant, and they can include binders such as povidone and surfactant, such as poloxamer, preferably Poloxamer 188. In some preferred embodiments of the present invention, povidone comprises from about 2 to about 2.5% w/w and preferably 2.13% w/w of a composition comprising irbesartan and diuretic such as hydrochlorothiazide. In another preferred embodiment of a composition comprising irbesartan and diuretic such as hydrochlorothiazide according to the present invention, the composition comprises povidone in an amount of from about 2 to about 2.5% w/w, more preferably 2.13% w/w of the composition, and poloxamer of from about 1 to about 1.2% w/w, more preferably 1.06% w/w of the composition.

[0030] Formulations containing irbesartan and diuretic can be prepared by any suitable method. A preferred method for forming a tablet formulation comprising irbesartan and hydrochlorothiazide according to one embodiment of the present invention is by a wet granulation process. By way of example, a formulation comprising irbesartan and hydrochlorothiazide can be prepared according to the following method:

- [0031] 1. Irbesartan and hydrochlorothiazide are mixed using high shear mixer.
 - [0032] 2. Pregelatinized Starch is mixed with the mixture of step 1 in high shear mixer.
 - [0033] 3. The mixture from step 2 is granulated with granulating solution of povidone in purified water using high shear mixer.
 - [0034] 4. The granules are dried in fluid bed dryer.
 - [0035] 5. The dried granules are sized by using oscillating granulator.
 - [0036] 6. The milled dried granulate is mixed with microcrystalline cellulose, croscarmellose sodium and silicon dioxide in a blender.
 - [0037] 7. The mixture of step 6 is mixed with magnesium stearate as a lubricant.
 - [0038] 8. The mixture from step 7 is mixed to form tablets using tablet press.
- [0039] By way of further example, a formulation comprising irbesartan and hydrochlorothiazide can be prepared according to the following method:
- [0040] 1. Irbesartan and hydrochlorothiazide are mixed using high shear mixer.
 - [0041] 2. The mixture of step 1 is partially granulated with a granulating solution of povidone in purified water using high shear mixer.
 - [0042] 3. Pregelatinized Starch is mixed with the mixture of step 2 in high shear mixer.
 - [0043] 4. The mixture from step 3 is granulated with granulating solution of Poloxamer 188 in purified water using high shear mixer.
 - [0044] 5. The granules are dried in fluid bed dryer.

[0045] 6. The dried granules are sized by using oscillating granulator.

[0046] 7. The milled dried granulate is mixed with microcrystalline cellulose, croscarmellose sodium and silicon dioxide in a blender.

[0047] 8. The mixture of step 7 is mixed with magnesium stearate as a lubricant.

[0048] 9. The mixture from step 8 is mixed to form tablets using tablet press.

[0049] The tablets comprising irbesartan and hydrochlorothiazide prepared from the compositions of the present invention preferably contain (per tablet), 150 mg of irbesartan and 12.5 mg of hydrochlorothiazide, or 300 mg of irbesartan and 12.5 mg of hydrochlorothiazide. Typically, the total weight of the tablet comprising 150 mg of irbesartan and 12.5 mg of hydrochlorothiazide is 188 mg and the total weight of the tablet comprising 300 mg irbesartan and 12.5 mg hydrochlorothiazide is 376 mg to 400 mg.

[0050] Preferred compositions according to the invention comprising irbesartan and hydrochlorothiazide are as follows:

Preferred Ingredients	Component	Concentration Range (% w/w)
Irbesartan	Active drug	75.0-79.79
Hydrochlorothiazide	Active drug	3.32-6.65
Pregelatinized starch (starch 1500)	Binder	3.19-5.32
Povidone (PVP K-30)	Binder	2.0-2.15
Microcrystalline Cellulose (Avicel PH 102)	Diluent	5.56-5.96
Croscarmellose Sodium (Ac-Di-Sol)	Disintegrant	3.19-4.0
Silicon Dioxide (syloid 244)	Antiadherent	0.4-0.43
Magnesium Stearate	Lubricant	1.0-1.06

[0051] The following examples are presented to illustrate certain features of the invention, but these should not be understood to limit the scope of the invention.

EXAMPLE 1

[0052] This example illustrates the preparation of tablets containing 75% irbesartan.

[0053] Tablets containing irbesartan were prepared in three potencies using the composition of the present invention described in Table 2

[0054] 1. 75 mg irbesartan with a total weight of 100 mg per tablet.

[0055] 2. 150 mg irbesartan with total weight of 200 mg per tablet.

[0056] 3. 300 mg irbesartan with a total weight of 400 mg per tablet.

TABLE 2

Ingredients	Component	Concentration (% w/w)
Irbesartan	Active drug	75
Povidone (PVP K-30)	Binder	2.0
Pregelatinized Starch (Starch 1500)	Binder	8.0
Poloxamer 188	Surfactant	2.0

TABLE 2-continued

Ingredients	Component	Concentration (% w/w)
Microcrystalline Cellulose (Avicel PH 102)	Diluent	7.5
Croscarmellose Sodium (Ac-Di-Sol)	Disintegrant	4.0
Silicon Dioxide (syloid 244)	Antiadherent	0.5
Magnesium Stearate	Lubricant	1.0
Total	100.0	100.0

[0057] Using the above formulation, tablets were prepared by an aqueous wet granulation process, in accordance with the method described above. The partial granulation of irbesartan with granulating solution of povidone in purified water was carried out in a high shear mixer (Diosna). This mixture was mixed with pregelatinized starch and then granulated with the granulating fluid of Poloxamer 188 in purified water. The granules obtained were dried in a fluid bed dryer until the loss-on-drying (LOD) was 1.5% or less. The dried granules were passed through an oscillating granulator. The milled granulates were mixed with the microcrystalline cellulose, croscarmellose sodium and silicon dioxide in a blender. The blend obtained was then mixed with magnesium stearate. By compressing the mixture using tableting equipment, tablets were prepared for each potency having the composition as shown in Table 3.

TABLE 3

Ingredients	75 mg potency (mg)	150 mg potency (mg)	300 mg potency (mg)
Irbesartan	75.0	150.0	300.0
Povidone (PVP K-30)	2.0	4.0	8.0
Pregelatinized Starch (Starch 1500)	8.0	16.0	24.0
Poloxamer 188	2.0	4.0	8.0
Microcrystalline Cellulose (Avicel PH 102)	7.5	15.0	30.0
Croscarmellose Sodium (Ac-Di-Sol)	4.0	8.0	16.0
Silicon Dioxide (syloid 244)	0.5	1.0	2.0
Magnesium Stearate	1.0	2.0	4.0
Total tablet weight	100.0	200.0	400.0

[0058] Tablets of each potency were tested for dissolution according to the U.S. Pharmacopeia, using USP apparatus 2 and placing the tablet in 1000 ml of 0.1 hydrochloric acid at 37° C. with paddle speed of 50 rpm. The dissolution results are set forth in Table 3A.

TABLE 3A

Dissolution Results In %		
Time In Minutes	% Dissolve	% Dissolve
5	79	77
10	92	86
20	97	95
30	98	97

EXAMPLE 2

[0059] This example illustrates the preparation of tablets containing 80% irbesartan.

[0060] Tablets containing irbesartan were prepared in these potencies from the composition of present invention describe in Table 4.

[0061] 75 mg irbesartan with a total weight of 94 mg per tablet.

[0062] 150 mg irbesartan with a total weight of 188 mg per tablet.

[0063] 300 mg irbesartan with a total weight of 376 mg per tablet.

TABLE 4

Ingredients	Component	Concentration (% w/w)
Irbesartan	Active drug	79.79
Povidone (PVP K-30)	Binder	2.13
Pregelatinized starch (Starch 1500)	Binder	6.38
Poloxamer 188	Surfactant	1.06
Microcrystalline Cellulose (Avicel PH 102)	Diluent	5.56
Croscarmellose Sodium (Ac-Di-Sol)	Disintegrant	3.19
Silicon Dioxide (Syloid 244)	Antidherent	0.43
Magnesium Stearate	Lubricant	1.06
Total	100%	100.0

[0064] Using the above formulation the tablets were prepared by a wet granulation process as a method analogous to that of Example 1. The composition of this formulation is presented in Table 5.

TABLE 5

Ingredients	75 mg potency (mg)	150 mg potency (mg)	300 mg potency (mg)
Irbesartan	75.1	150.0	300.0
Povidone (PVP K-30)	2.1	4.0	8.0
Pregelatinized Starch (Starch 1500)	6.3	12.0	24.0
Poloxamer 188	1.0	2.0	4.0
Microcrystalline Cellulose (Avicel PH 102)	5.6	11.2	22.4
Croscarmellose Sodium (Ac-Di-Sol)	3.1	6.0	12.0
Silicon Dioxide (syloid 244)	0.4	0.8	1.6
Magnesium Stearate	1.1	2.0	4.0
Total tablet weight	94.3	188.0	376.0

[0065] Tablets of each potency were tested for dissolution according to the U.S. Pharmacopeia, using USP apparatus 2 and placing the tablet in 1000 ml of 0.1 hydrochloric acid at 37° C. with paddle speed of 50 rpm. The % irbesartan in the formulation dissolved over time is set forth in Table 5A.

TABLE 5A

Dissolution Results In %			
Time In Minutes	% Dissolve	% Dissolve	% Dissolve
5	79	80	84
10	93	90	95
20	100	96	99
30	102	98	99

EXAMPLE 3

[0066] This example illustrates the preparation of tablets comprising irbesartan in an amount of approximately 80% by weight of the formulation, and hydrochlorothiazide in an amount of approximately 3.32% -6.65% by weight of the formulation.

[0067] Tablets containing irbesartan and hydrochlorothiazide were prepared in various potencies in accordance with the present invention as described in Table 6.

[0068] The tablets a) comprise 150 mg irbesartan and 12.5 mg hydrochlorothiazide with a total weight of 188 mg per tablet and b) comprise 300 mg irbesartan and 12.5 mg hydrochlorothiazide with a total weight of 376 mg per tablet.

TABLE 6

Ingredients	Component	Concentration (% w/w)	Concentration (% w/w)
Irbesartan	Active drug	79.79	79.79
Hydrochlorothiazide	Active drug	6.65	3.32
Pregelatinized Starch (Starch 1500)	Binder	3.19	4.12
Povidone (PVP K-30)	Binder	2.13	2.13
Microcrystalline Cellulose (Avicel PH 102)	Diluent	3.56	5.96
Croscarmellose Sodium (Ac-Di-Sol)	Disintegrant	3.19	3.19
Silicon Dioxide (syloid 244)	Antidherent	0.43	0.43
Magnesium Stearate	Lubricant	1.06	1.06
Total	100.0	100.0	100.0

[0069] Using the above formulation, tablets were prepared by wet granulation. Irbesartan and hydrochlorothiazide were mixed in a high shear mixer (Diosna). This mixture was mixed with pregelatinized starch and then granulated with the granulating fluid of povidone in purified water. The granules obtained were dried in a fluid bed dryer until the loss-on-drying (LOD) is 1.5% or less. The dried granules were passed through an oscillating granulator. The milled granulates were mixed with the microcrystalline cellulose, croscarmellose sodium and silicon dioxide in a blender. The blend obtained was then mixed with magnesium stearate. By compressing the mixture using tableting equipment, tablets were prepared for each potency having the composition as shown in the table above.

EXAMPLE 4

[0070] This example illustrates another formulation containing irbesartan and hydrochlorothiazide in accordance with the invention. The formulations were made by wet granulation, as described above.

TABLE 7

Ingredients	150 mg/12.5 mg potency (mg)	300 mg/12.5 mg potency (mg)
Irbesartan	150.0	300.0
Hydrochlorothiazide	12.5	12.5
Pregelatinized Starch (Starch 1500)	6.0	15.5
Povidone (PVP K-30)	4.0	8.0
Microcrystalline Cellulose (Avicel PH 102)	6.7	22.4
Croscarmellose Sodium (Ac-Di-Sol)	6.0	12.0

TABLE 7-continued

Ingredients	150 mg/12.5 mg potency (mg)	300 mg/12.5 mg potency (mg)
Silicon Dioxide (syleid 244)	0.8	1.6
Magnesium Stearate	2.0	4.0
Total tablet weight	188.0	376.0

EXAMPLE 5

[0071] This example illustrates another formulation containing irbesartan and hydrochlorothiazide in accordance with the invention. The formulations were made by wet granulation as described above.

TABLE 8

Ingredients	300 mg/12.5 mg potency (mg)	Concentration (% w/w)	150 mg/12.5 mg potency (mg)	Concentration (% w/w)
Irbesartan	300.0	79.79	150	79.79
Hydrochlorothiazide	12.5	3.32	12.5	6.65
Pregelatinized Starch (Starch 1500)	12.0	3.19	6.0	3.19
Povidone (PVP K-30)	8.0	2.13	4.0	2.13
Microcrystalline Cellulose (Avicel PH 102)	19.9	5.29	3.7	1.96
Croscarmellose Sodium (Ac-Di-Sol)	18.0	4.79	9.0	4.79
Silicon Dioxide (syleid 244)	1.6	0.43	0.8	0.43
Magnesium Stearate	4.0	1.06	2.0	1.06
Total tablet weight	376.0	100.0	188.0	100.0

EXAMPLE 6

[0072] This example illustrates another formulation containing irbesartan and hydrochlorothiazide in accordance with the invention. The formulations were made by wet granulation as described above.

TABLE 9

Ingredients	150 mg/12.5 mg potency (mg)	Concentration (% w/w)	300 mg/12.5 mg potency (mg)	Concentration (% w/w)
Irbesartan	150.0	79.79	300.0	79.79
Hydrochlorothiazide	12.5	6.65	12.5	3.32
Pregelatinized Starch (Starch 1500)	6.0	3.19	12.0	3.19
Povidone (PVP K-30)	4.0	2.13	8.0	2.13
Poloxamer 188	2.0	1.06	4.0	1.06
Microcrystalline Cellulose (Avicel PH 102)	3.7	1.97	19.9	5.29
Croscarmellose Sodium (Ac-Di-Sol)	7.0	3.72	14.0	3.72
Silicon Dioxide (syleid 244)	0.8	0.43	1.6	0.43
Magnesium Stearate	2.0	1.06	4.0	1.06
Total	188.0	100.0	376.0	100.0

[0073] All references, including publications, patent applications, and patents, cited herein are hereby incorporated by reference to the same extent as if each reference were individually and specifically indicated to be incorporated by reference and were set forth in its entirety herein. Also, reference herein to other publications is not an admission that such publications constitute prior art to this application.

[0074] Preferred embodiments of this invention are described herein, including the best mode known to the inventors for carrying out the invention. Variations of those preferred embodiments may become apparent to those of ordinary skill in the art upon reading the foregoing description. The inventors expect skilled artisans to employ such variations as appropriate, and the inventors intend for the invention to be practiced otherwise than as specifically described herein. Accordingly, this invention includes all modifications and equivalents of the subject matter recited in the claims appended herein as permitted by applicable law. Moreover, any combination of the above-described elements in all possible variations thereof is encompassed by the invention unless otherwise indicated herein or otherwise clearly contradicted by context.

What is claimed is:

1. A composition comprising greater than 70% w/w irbesartan and at least one pharmaceutically-acceptable excipient.
2. The composition of claim 1, which exhibits a dissolution profile according to which greater than about 85% of the irbesartan is dissolved within about 30 minutes using USP apparatus 2, placing the tablet in 1000 mL of 0.1N hydrochloric acid at 37° C. with paddle speed of 50 rpm.
3. A composition comprising greater than 70% w/w irbesartan, wherein said composition exhibits a dissolution profile according to which greater than about 85% of the irbesartan is dissolved within about 30 minutes using USP apparatus 2, placing the tablet in 1000 mL of 0.1N hydrochloric acid at 37° C. with paddle speed of 50 rpm.
4. The composition of claim 3, which comprises greater than 75% w/w irbesartan and at least one pharmaceutically acceptable excipient.
5. The composition of claim 1, in the form of a tablet.
6. The composition of claim 1, wherein said composition comprises a binder.
7. The composition of claim 6, wherein a binder is povidone or pregelatinized starch.
8. The composition of claim 7, wherein a binder is povidone.
9. The composition of claim 8, wherein the povidone is from about 1.0 to about 7.0% w/w of the composition.
10. The composition of claim 9, wherein a binder is pregelatinized starch (starch 1500).
11. The composition of claim 10, wherein the pregelatinized starch (starch 1500) is from about 1.0 to about 10.0% w/w of the composition.
12. The composition of claim 1, wherein said composition comprises a disintegrant.
13. The composition of claim 12 wherein a disintegrant is croscarmellose sodium.
14. The composition of claim 13, wherein the croscarmellose sodium is Ac-Di-sol and is from about 1.0 to about 7.0% w/w of the composition.
15. The composition of claim 1, wherein said composition comprises a surfactant.
16. The composition of claim 15, wherein a surfactant is poloxamer 188.
17. The composition of claim 16, wherein the poloxamer 188 is from about 0.2 to about 6.0% w/w of the composition.
18. The composition of claim 1, wherein said composition comprises a diluent.
19. The composition of claim 18, wherein said diluent is microcrystalline cellulose.
20. The composition of claim 19, wherein the microcrystalline cellulose is Avicel PH 102 FMC and comprises from about 2.0 to about 10.0% w/w of the composition.
21. The composition of claim 1, wherein said composition comprises an antiadherent.
22. The composition of claim 21, wherein the antiadherent is silicon dioxide.
23. The composition of claim 22, wherein the silicon dioxide is syloid 244 and comprises from about 0.4% w/w to about 0.5% w/w of the composition.
24. The composition of claim 1, wherein said composition comprises a lubricant.
25. The composition of claim 24, wherein said lubricant is magnesium stearate.
26. The composition of claim 25, wherein the magnesium stearate comprises from about 0.2 to about 2.0% w/w of the composition.
27. The composition of claim 1, further wherein said composition comprises at least one additional active pharmaceutical agent.
28. The composition of claim 27, wherein an additional active pharmaceutical agent is a diuretic agent.
29. The composition of claim 27, wherein an additional active agent is hydrochlorothiazide.
30. The composition of claim 1, wherein the composition comprises, by weight, 75% irbesartan, and by weight, about 10% binder, about 7.5% diluent, about 4% disintegrant, about 2% surfactant, about 1% lubricant, and about 0.5% antiadherent; wherein said binder consists of pregelatinized starch and povidone; said diluent is microcrystalline cellulose, said disintegrant is croscarmellose sodium, said surfactant is poloxamer 188, said lubricant is magnesium stearate, and said antiadherent is silicon dioxide.
31. The composition of claim 30, wherein said composition is a tablet, and the tablet has a dissolution such that greater than 85% of the irbesartan contained therein dissolves within 30 minutes under the following conditions: USP apparatus 2, placing the tablet in 1000 mL of 0.1N hydrochloric acid at 37° C. with paddle speed of 50 rpm.
32. The composition of claim 1, wherein the composition comprises, by weight, 79.79% irbesartan, and the pharmaceutical excipients comprise, by weight, about 8.5% binder, about 5.9% diluent, about 3.1% disintegrant, about 1% surfactant, about 1% lubricant, and about 0.5% antiadherent; wherein said binder consists of pregelatinized starch and povidone; said diluent is microcrystalline cellulose, said disintegrant is croscarmellose sodium, said surfactant is poloxamer 188, said lubricant is magnesium stearate, and said antiadherent is silicon dioxide.
33. The composition of claim 32, wherein said composition is a tablet, such that the tablet has a dissolution performance such that greater than 85% of the irbesartan contained therein dissolves within 30 minutes under the following conditions: USP apparatus 2, placing the tablet in 1000 mL of 0.1N hydrochloric acid at 37° C. with paddle

speed of 50 rpm. The tablet of claim 9, wherein the tablet is prepared by a wet granulation method.

34. The composition of claim 1, which exhibits a dissolution profile according to which greater than about 80% of the irbesartan is dissolved within about 10 minutes using USP apparatus 2, placing the tablet in 1000 mL of 0.1N hydrochloric acid at 37° C. with paddle speed of 50 rpm.

35. The composition of claim 1, which exhibits a dissolution profile according to which greater than about 85% of the irbesartan is dissolved within about 10 minutes using USP apparatus 2, placing the tablet in 1000 mL of 0.1N hydrochloric acid at 37° C. with paddle speed of 50 rpm.

36. The composition of claim 1, which exhibits a dissolution profile according to which at least about 75% of the irbesartan is dissolved within about 5 minutes, at least about 85% of the irbesartan is dissolved within about 10 minutes, and at least about 95% of the irbesartan is dissolved within about 20 minutes using USP apparatus 2, placing the tablet in 1000 mL of 0.1N hydrochloric acid at 37° C. with paddle speed of 50 rpm.

37. The composition of claim 1, wherein the composition comprises, by weight, 79.79% irbesartan, from about 3% to about 7% hydrochlorothiazide, from about 5.3% to about 7.5% binder, from about 3.5% to about 6% diluent, from

about 3% to about 3.2% disintegrant, from about 1% to about 1.1% lubricant, and from about 0.4% to about 0.5% antiadherent; wherein said binder consists of pregelatinized starch and povidone; said diluent is microcrystalline cellulose, said disintegrant is croscarmellose sodium, said lubricant is magnesium stearate, and said antiadherent is silicon dioxide.

38. The composition of claim 36, wherein the composition comprises, by weight, 79.79% irbesartan, 2.13% povidone, 6.38% pregelatinized starch, 3.15% croscarmellose sodium, 1.01% poloxamer 188, 5.96% microcrystalline cellulose, 1.01% magnesium stearate and 0.43% silicon dioxide.

39. The composition of claim 37, wherein the composition comprises 150 mg of irbesartan and 12.5 mg of hydrochlorothiazide.

40. The composition of claim 37, wherein the composition comprises, by weight, about 79% irbesartan, about 3.3% hydrochlorothiazide, about 3.1% pregelatinized starch, about 2.1% povidone, about 5.3% microcrystalline cellulose, about 4.7% croscarmellose sodium, about 0.4% silicon dioxide and about 1% magnesium stearate.

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